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PSYCHOPHARMACOLOGY ABSTRACTS

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ABSTRACTS

PRECLINICAL PSYCHOPHARMACOLOGY

01 CHEMICAL SYNTHESIS, ISOLATION AND CHARACTERIZATION

089786 Eriksoo, Edgar; Rohte, Oskar. Aktiebolaget Leo, Halsingborg, Sweden Chemistry and pharmacology of a new potential antidepressant, N-Methyl-N-(4-chlorobenzyl-methyl)-3-(10, 11-dihydro-5H-dibenz (b,f) azepin-5-yl)-propylamine hydrochloride) (leo 640, lopraminehydrochloride). *Arzneimittel-Forschung (Aulendorf/Wurtt).* 20(10):1561-1569, 1970.

The synthesis, physicochemical properties and pharmacological evaluation of a new, potential antidepressant, N-methyl-N-(4-chlorobenzoyl-methyl)-3-(10,11-dihydro-5H-dibenz (b,f) azepin-5-yl)-proplamine hydrochloride (Leo 640). Leo 640 is an analogue of imipramine and desipramine. When compared pharamcologically with these and other tricyclic antidepressants, Leo 640 shows itself qualitatively and quantitatively similar in antidepressant effects to desipramine. The acute and intermediate term toxicity of Leo 640 was found to be very low. Preliminary studies in man have shown encouraging results. It is suggested that Leo 640 may represent a useful advance in antidepressant therapy and is worthy of further study. 48 references. (Author abstract modified)

090426 Ho, Beng T.; Li, Ko-Chin; Walker, K. E.; Tansey, L. Wayne; Kralik, Patricia M.; McIsaac, William M. Texas Research Institute of Mental Sciences, Houston, Texas 77025 Inhibitors of monoamine oxidase VI: effects of substitution on inhibitory activity of 6 (or 8)-substituted beta-carbolines. *Journal of Pharmaceutical Sciences.* 59(10):1445-1448, 1970.

A number of 6(or 8) substituted aromatic beta-carbolines were synthesized, and their inhibitory activities toward monoamine oxidase were compared with their tetrahydro congeners. A considerable difference in the effects of 6(or 8)-substitution on the inhibitory activities existed between these aromatic and tetrahydro-beta -carbolines. Influence of 9-methyl substitution on activities was greater with the tetrahydro than the aromatic series; as a result, 9 -methyltetrahydro-beta-carbolines were generally much better inhibitors of the enzyme than the corresponding 9-hydrogen-tetrahydro -beta-carbolines. An amino group at C1 of beta-carboline caused a fivefold decrease in inhibitory activity. This decrease was likely due to the steric hindrance by the bulk of the amino group. Aromatic beta-carbolines were prepared by the palladium on charcoal catalyzed dehydrogenation of the corresponding tetrahydro-beta-carbolines. Methylation of the N9 of aromatic beta-carboline was carried out with methyl iodide in the presence of sodium hydride. Nitration of beta -carboline gave a mixture of 2 isomeric products, 6-nitro-beta -carboline and 8-nitro-beta-carboline, which were separated with hot chloroform. Catalytic reduction converted the nitro compounds to 6-nitro-beta-carboline and 8-amino-beta-carboline, respectively. The positions of the amino group was confirmed by NMR spectrometry. 9 references. (author abstract)

092209 Gardner, Frank T.; DeBold, Richard G.; Firshein, William; Heermans, Harry W., Jr. Department of Biology, Yale University, New Haven, Connecticut Increased incorporation of 14C-uridine into rat brain RNA as a result of novel electroshock. *Nature (London).* 227(5264):1242-1243, 1970.

Electroshock laboratory experiments with rats were conducted both to isolate the elements of a learning situation and to correlate the elements with observed changes in RNA concentrations in the brain. Findings indicate that brain RNA stimulation is likely to result from a shock stress response that is reduced if the animals become habituated to the shock by prior exposure to it. Electric footshock was administered to rats at levels previously used as aversive stimuli in avoidance training. The brain RNA synthesis rate was compared in 2 groups exposed to shock and the control group not shocked. Twenty four hours after the first stimulus was administered to only 1 group, all groups received 10 microliters of 14C-uridine injected into the ventricles, the 2 experimental groups were shocked, and all were decapitated for examination. 8 references.

092888 Martin, Ned H.; Pitt, Colin G.; Wall, Monroe E.; Wildes, Julia W. Research Triangle Institute, Post Office Box 12194, Research Triangle Park, North Carolina 27709 The synthesis and biological activity of (-)-delta9(11)-trans-tetrahydrocannabinol; a new procedure for the cleavage of phenyl methyl ethers (Unpublished paper). North Carolina, 1970. 4 p.

A new procedure for the cleavage of phenyl methyl ethers in a study on the synthesis and biological activity of (-)-delta9(11)-trans-tetrahydrocannabinol (THC) is reported. This compound provides a key intermediate for the introduction of new functionalities at either carbon 9 or carbon 11. For biological studies, it is desirable to have a ready source of the optically active isomer of the natural configuration of delta9(11)-THC. A method was sought to convert readily available delta8 or delta9-isomers to this compound. Demethylation of the methyl ether to the free phenol was accomplished with potassium thiophenoxide in diethylene glycol. Relatively weak psychotomimetic properties are exhibited by delta9(11)-THC when the compound is administered intravenously to mice. It is believed that delta9(11)-THC shows promise as a useful synthetic intermediate in cannabinoid chemistry. 12 references.a

093550 Razdan, Raj K.; Handrick, G. Richard. Center for Studies of Narcotics and Drug Abuse, National Institute of Mental Health, Bethesda, Maryland 20014 Hashish: a stereospecific synthesis of (-)-delta 1- and (-)-delta 1(6)-tetrahydrocannabinols (Unpublished paper). Bethesda, Maryland, NIMH, 1970. 5 p.

As one phase of research on hashish, a stereospecific synthesis of (-)-delta 1-tetrahydrocannabinol (THC) and (-)-delta 1(6)-THC is performed. This 1 step stereospecific synthesis via carane derivatives leads first to (-)-delta(6)-THC and hence to (-)-delta 1-THC. A slight change in experimental conditions also provides the first 1 step synthesis of delta 1-THUC of high optical activity. The scheme of synthesis and details of the procedure are presented. Conditions used and percentages of delta 1-trans-THC and delta 1-cis-THC synthesized are discussed. No cannabidiol was formed in any of the reactions. Further work along these lines is in progress. 12 references.

094623 Nodiff, Edward A.; Tanabe, Keiichi; Schnierle, Franz; Morosawa, Shiro; Hoffman, Thomas W.; Takada, Katsuhiko; Manian, Albert A. The Research Institute of Temple University, Philadelphia, Pa. Synthesis of possible metabolites of chlorpromazine. III. 7,8-disubstituted chlorpromazine derivatives. *Journal of Heterocyclic Chemistry*. 7:203-208, 1970.

A note reports the preparation of 7-hydroxy-8-chlorpromazine and its nor-1 and nor-2 derivatives. These compounds are part of a series of 3-, 7-, 8-, and 9-hydroxychlorpromazine and their 7, 8-disubstituted derivatives. 23 references.

095700 Barfknecht, Charles F. College of Pharmacy, University of Iowa, Iowa City, Iowa, 52240 Absolute configurations of methoxylated amphetamines. Final Report, NIMH Grant MH-16379, 1970. 13 p.

In the research proposal, 3 areas were to be explored: a) resolution of methoxylated amphetamines, b) degradation of methoxylated amphetamines to amphetamines, and c) determination of the optical rotation and assignment of absolute configurations. The following results were accomplished: a) one methoxylated amphetamine was successfully resolved into both the (+) and (-) enantiomers, b) an efficient method of ether cleavage giving high yields of hydroxylated amphetamines was developed, c) an extensive study of the model system reaction with 5-chloro-1- phenyltetrazole and the subsequent hydrogenolysis was made, and d) the pitfalls associated with the extension of 3) to hydroxylated amphetamines were uncovered. 6 references. (Author abstract)

097582 Forrest, Irene S.; Brookes, Leonard G.; Holmes, Margot A.; Bacon, Virginia A.; Duffield, Allan M.; Solomon, Malcolm D. Stanford University School of Medicine, Stanford, California Preparation of 3H-7-hydroxychlorpromazine using sheep liver microsomes for hydroxylation of 3H-chlorpromazine. Final Report, NIMH Grant MH-18280, 1970. 10 p.

A terminal progress report is made on the preparation of 3H-7-hydroxychlorpromazine using sheep liver microsomes for hydroxylation of 3H-chlorpromazine. An in vitro production of more than 30% 7-hydroxychlorpromazine by sheep microsomes was demonstrated in an earlier interspecies study of 3H-chlorpromazine metabolism. The methods for isolation of sheep liver microsomes, preparation of the incubation medium containing tritium labelled chlorpromazine, and incubation of the microsomes are described. Thin layer chroatographic analysis and radioquantitation of the 3H-chlorpromazine metablism are described, also, and a tabular summary of the results of analyse of various incubations of fresh sheep liver microsomal preparation is presented.

Variations in the amounts of chlorpromazine metabolized and of 7-hydroxychlorpromazine produced are discussed in relation to animal age effect. In further studies, conditions of storage of the hepatic microsomes were varied to determine the effect on drug metabolizing pathways in an attempt to eliminate some of the pathways in favor of 7-hydroxylation. It was found that the pathways for hydroxylation are remarkably resistant to deterioration by storage and that storage condition manipulation could be used successfully for increasing the yields of some metabolites at the expense of others. A combination of prolonged frozen storage followed by limited refrigerated storage yielded 67.5% of 7-hydroxychlorpromazine, the highest yield obtained to date. A detailed procedure for the preparation of 3H-7-hydroxychlorpromazine is presented.

02 DRUG DEVELOPMENT (PRECLINICAL SCREENING)

089435 Roll, W. D. Department of Medicinal Chemistry, College of Pharmacy, University of Toledo, Toledo, Ohio 43606 Substituted benzamides with potential CNS-depressant and hypotensive activity. ***Journal of Pharmaceutical Sciences.*** **59(12):1838-1839, 1970.**

A series of 14 N-alkyl, N-aryl, and N-aralkyl analogs of N-cyclohexyl nitrobenzamide has been synthesized and characterized. The compounds have been studied for their ability to depress the spontaneous motor activity of mice and for their hypotensive activity in rats. Four of the compounds, which are structurally characterized by small alkyl groups attached to the amide nitrogen and a p-nitro group, showed the greatest central nervous system depressant activity. The hypotensive action of these compounds paralleled their depressant action. 2 references. (Author abstract)

089789 Mutsuda, Katsuichi. Dept. of Pharmacology, Niigata University School of Medicine, Tokyo, Japan Experimental studies on the effective procedure to inhibit the development of tolerance to and dependence on morphine. ***Arneimittel-Forshung (Aulendorf/Wurtt).*** **20(10):1596-1604, 1970.**

A study was made to find some substance which would inhibit the development of tolerance and dependence on morphine. Eleven phenothiazine derivatives and caffeine were tested for their effect on the analgesic potency of morphine and the development of morphine tolerance. The study was conducted with rats and monkeys. Of all the drugs considered potentially useful because of their chemical structure, only caffeine and 3-methylsulfonyl-10-2-(1-methyl-2-piperidyl)-ethyl-phenothiazine (TPN-12) were found effective. In rats, these 2 drugs increase the analgesic potency of morphine and inhibit the development of morphine tolerance; prior induced tolerance is temporarily arrested and the disappearnce of tolerance is accelerated. In monkeys, TPN-12 increases the depressant action of morphine, inhibits the development of physical and psychic dependence, arrests previously induced tolerance, and induces spasms in animals with withdrawal symptoms. The theoretical significance of these findings as related to the mechanism of the action of morphine is discussed. 18 references. (Author abstract modified)

03 MECHANISM OF ACTION: PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

089436 Burke, David H.; Mann, David E., Jr. School of Pharmacy, Temple University, Philadelphia, Pennsylvania 19104 Influence of several autonomic drugs on sodium nitroprusside and oxotremorine-induced hypothermia in immature and mature mice. ***Journal of Pharmaceutical Sciences.*** **59(12):1814-1818, 1970.**

The influence of several autonomic drugs on sodium nitroprusside and oxotremorine induced hypothermia is determined in immature and mature mice. It was shown that sodium nitroprusside and oxotremorine each produced body temperature depression that was independent of age. Atropine inhibited oxotremorine hypothermia in both age groups, but was ineffective in modifying thermal responses to nitroprusside in both age categories. Pilocarpine administration did not alter oxotremorine activity at either age level, while nitroprusside hypothermia was enhanced and partially reversed, respectively, in immature and mature mice. Nicotine and tetraethylammonium chloride were unable to modify hypothermia produced by oxotremorine and nitroferricyanide in adult mice. Nicotine enhanced nitroprusside hypothermia in 10 day old mice, while temperature depression due to oxotremorine was unaffected in the same age group. Administration of tetraethylammonium chloride to immature animals

treated with oxotremorine and nitroprusside resulted in greater temperature depression. Chlorpromazine, which produced no change in oxotremorine or nitroprusside hypothermia in 10 day old mice, partially blocked oxotremorine induced hypothermia in mature animals; the weak parasympatholytic phenothiazine produced no significant difference in hypothermia when given prior to nitroprusside in the adult group. 14 references. (Author abstract modified)

089439 Ho, Beng T.; Estevez, Vicente; McIsaac, William M. Texas Research Institute of Mental Sciences, Houston, Texas 77025 Effect of vehicles on metabolism of serotonin and imipramine. ***Journal of Pharmaceutical Sciences.*** **59(12):1780-1782, 1970.**

The effects of different vehicles on excretion and metabolism of serotonin and imipramine are studied. While water is the most common vehicle for the administration of drugs for pharmacological studies in animals, other solvents are also frequently used, and a study was planned to determine the difference in effects of water and 2 organic solvents as vehicles on the metabolism of 2 14C labelled centrally acting agents. Rats receiving serotonin-14C in dimethyl sulfoxide or propylene glycol excreted radioactivity in the urine slower and in lesser amounts than when water was the vehicle. However, the urinary excretion of radioactivity by rats administered a single dose of imipramine-14C was the same for the 3 vehicles over a period of 72 hr. Dimethyl sulfoxide and propylene glycol caused not only an increase in the amount of urinary 5-hydroxytryptophol and N-acetylserotonin, but also an increase in the conjugated form of these 2 metabolites as well as that of 5-hydroxyindoleacetic acid. These two nonaqueous vehicles caused a diminished demethylation of imipramine when compared to the water vehicle. 9 references. (Author abstract modified)

089547 Reynier, M. Institut de Biologie Physico-Chimique, Laboratoire de Biospectroscopie, 13, rue Pierre-et-Marie Curie, Paris 5, France /A study of hepatic alcohol dehydrogenase inhibition (ADH) induced by pyrazol: II. the role of liver ADH in the in vivo metabolism of hydroxyl compounds./ Etude de l'inhibition de l'alcool deshydrogenase (ADH) du foie par le pyrazole: II. mise en evidence du role de l'ADH du foie dans le metabolisme de substances hydroxylees in vivo. ***Agressologie (Paris).*** **11(5):407-416, 1970.**

In a study of hepatic alcohol dehydrogenase (ADH) inhibition-induced by pyrazol, the role of liver ADH in the in vivo metabolism of hydroxyl compounds was studied. It was found that pyrazol and 4-bromopyrazol prolong in the mouse sleeping time induced by hexobarbital. The plamastic concentration of hexobarbital in rats is greater 90 min after injection if they were treated earlier with pyrazol. Pyrazol and 4-bromopyrazol, on the other hand, inhibit in the rat the urenary excretion of 4-nitrotoluene metabolites (4-nitro and 4-aminobenzoic acids). The comparison of the pyrazol and 4-bromopyrazol doses used in the study with those that effect ethanol oxidation and with their inhibition constants of ADH in vitro, shows that their action of hexobarbital and 4-nitrotoluene is due to the ADH inhibition. These results prove that in vivo hepatic ADH plays a part not only in the metabolism of exogenous alcohols, but also in the metabolism of drugs that can be hydroxylated in the liver under the action of the microsomal enzyme system which metabolizes drugs. 22 references. (Journal abstract modified)

089548 Reynier, M. Institut de Biologie, Laboratoire de Biospectroscopie, 13, rue Pierre et Marie Curie, Paris 5, France /A study of hepatic alcohol dehydrogenase inhibition induced by pyrazol: I. in vivo action on ethanol and 2-phenylethanol./ Etude de l'inhibition de l'alcool deshydrogenase du foie par le pyrazole: I. effet sur le metabolisme de l'ethanol et de l'alcool phenyl-2-ethylique in vivo. ***Aggressologie (Paris).*** **11(5):401-406, 1970.**

In vitro, pyrazol and 4-bromopyrazol are strong inhibitors of alcohol dehydrogenase (ADH) of rat liver; a study shows that, in vivo, pyrazol and 4-bromopyrazol decrease ethanol oxidation in the rat. The action of various inhibiting doses was studied, along with the effect of delay between administration and ethanol intake. The ADH inhibition in vivo caused by pyrazol is also revealed by prolongation of sleeping time obtained with 2-phenylethanol. 13 references. (Journal abstract modified)

090134 Marcucci, F.; Fanelli, R.; Mussini, E.; Garattini, S. Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea, 62-20157 Milan, Italy Effect of phenobarbital on the in vitro metabolism of diazepam in several animal species. ***Biochemical Pharmacology.*** **19(5):1771-1776, 1970.**

The metabolic pathway by which diazepam is transformed in vitro by liver microsomes from control and phenobarbital treated rats, mice and guinea pigs was studied in detail. Rats, mice and guinea pigs were given 40mg/kg i.p.,b.i.d.,phenobarbital for 4 days. Sacrificed one day after the last injection, the livers were removed, weighed, chilled, homogenized, and analyzed for diazepam metabolites. It was found that increased diazepam metabolism resulting from phenobarbital treatment led to the formation of increased amounts of hydroxylated metabolites in mice, and of both hydroxylated and N-demethylated metabolites in rats. In guinea pigs pretreatment with phenobarbital produced only an increased formation of N-demethylated metabolite. In all the animal species considered, in addition to the increased diazepam metabolism, phenobarbital treatment led to a decreased recovery of diazepam from incubation medium. 11 references. (author abstract modified)

090136 Lippmann, W. Biogenic Amines Laboratory, Ayerst Laboratories, Montreal, Quebec, Canada Blockade of norepinephrine uptake and related activities of cis- and trans-N,N(prime)-bis-(1-naphthylmethyl)-1,4-cyclohexane Bis-(methylamine) dihydrochloride. *Biochemical Pharmacology.* 19(5):1709-1717, 1970.

The effects of cis- (C; AY-20,552) and trans- (T; AY-20,553) N,N(prime)-bis (1-naphthylmethyl)-1,4-cyclohexane bis(methylamine) dihydrochloride on the uptake and storage of the monoamines and their related properties were determined. Both compounds reduced the 3H-norepinephrine (3H-NE) in the mouse and rat heart when given before, but not after, the 3H-NE; T was more potent in its action. The uptake activity was largely recovered by 7 hr after C, 16 hr after T or imipramine, and 24 hr after desmethylimipramine. C and T reduced the norepinephrine depleting activity of metaraminol and alpha-methyl-metatyrosine. Neither compound prevented the norepinephrine depletion, tremors or lacrimation caused by tremorine. C and T did not cause any, or caused only partial, antagonism, whereas imipramine reversed the sedation, decreased locomotor activity and blepharospasm caused by tetrabenazine. C (.0000005M) and T (.00005M) inhibited the free fatty acid mobilization in vitro induced by norepinephrine. 25 references. (author abstract)

090139 Frank, G. B.; Jhamandas, K. Department of Pharmacology, University of Alberta, Edmonton, Alberta, Canada Effects of drugs acting alone and in combination on the motor activity of intact mice. *British Journal of Pharmacology (London).* 39(4):696-706, 1970.

The effects of centrally acting drugs and of various central nervous system stimulants were tested in order to compare their effects with those of previously studied anesthetics. When administered to intact white mice, the central depressants diphenhydramine, promethazine, chlorpromazine, gammahydroxybutyrate, gammabutyrolactone, hyoscine, and pethidine produced sedation in small doses, but excitement and convulsions in higher doses. When given to mice pretreated with subanesthetic doses of phenobarbitone these drugs abolished the righting reflex both in convulsant doses (hyoscine excepted) and in nonconvulsant doses. These effects are similar to the effects previously observed with local anesthetics. Meprobamate, diazepam and chlorpromazine produced a loss of righting reflex both when given alone and following phenobarbitone. When given alone in higher doses, chlorpromazine induced convulsions. The central stimulants bemegride and picrotoxin antagonized the loss of righting reflex produced by phenobarbitone, but nikethamide, caffeine and strychnine did not alter the depressant effects of phenobarbitone. On the basis of these and previous studieswith intact white mice a tentative classification of drugs having generalized depressant and stimulant effects on the central nervous system was proposed and discussed. 8 references. (author abstract modified)

090147 Simon, E. J.; Rosenberg, P. Department of Medicine, New York University School of Medicine, New York, New York 10016 Effects of narcotics on the giant axon of the squid. *Journal of Neurochemistry (London).* 17(7):881-887, 1970.

Levorphanol (.001M) reversibly blocked conduction in the giant axon of the squid and axons from the walking legs of spider crab and lobster. Similar concentrations of levallorphan and dextrorphan blocked conduction in the squid giant axon. Under the same experimental condition morphine caused an approximately 40 percent decrease in spike height. Levorphanol did not affect the resting potential or resistance of the squid axon. Spermidine, spermine and dinitrophenol had little or no direct effect on the action potential

nor did they alter the potency of levorphanol. Concentrations of levorphanol as low as .00005M blocked repetitive or spontaneous activity in the squid axon induced by decreasing the divalent cations in the medium. After exposure to tritiated levorphanol, the axoplasm and envelope of the squid axon accumulated up to 500 percent of the concentration of tritium found in the external medium, dependent on time of exposure, and other variables. At pH 6 the levels of penetration were 33 to 50 percent of those found at pH 8, which correlates with our observation that levorphanol is about 33 percent as potent in blocking the action potential at pH 6. The penetrability of levorphanol was not affected by spermidine, dinitrophenol or cottonmouth moccasin venom. Levorphanol did not alter the penetration of (C14)acetylcholine nor did it render the squid axon sensitive to it. The block of axonal conduction by compounds of the morphine series is discussed both as to possible mechanisms and significance. 20 references. (author abstract)

090148 Ghittoni, Nora E.; Ohlsson, W. G.; Sellinger, O. Z. Faculdad de Farmacia and Bioquimica, Universidad de Buenos Aires, Buenos Aires, Argentina The effect of methionine of the regional and intracellular disposition of (3H)-methionine sulphoximine in rat brain. *Journal of Neurochemistry (London).* 17(7):1057-1068, 1970.

The intracellular disposition of the convulsant agent, methionine sulphoximine (MSO), administered as methyl-labeled (3H)MSO, was examined in rat brain. Intraperitoneal (i.p.)and intrathecal (i.th.)routes were compared. The effect of simultaneous administration of methionine on the uptake, the regional distribution and the intracellular disposition of (3H)MSO was also assessed: (1) The peak uptake of i.p. (3H)MSO was at 2 hr and amounted to about 1 percent of the dose; the peak uptake of i.th. (3H)MSO was at 30 min postinjection and amounted to 40 percent of the administered dose. The uptake was effectively reduced when methionine was simultaneously administered. (2) The regional distribution of (3H)MSO as a function of time after injection revealed a rather uniform penetration of the entire brain by the drug. A maximum of 43 percent of the tissue radioactivity was found in the cerebellum 2 hr after i.p. injection, while 49 percent accumulated in the extracortical portion of the brain 3.5hr after i.th. administration. Methionine did not affect the regional distribution of (3H)MSO. (3) Differential centrifugation of samples of cortex and cerebellum revealed an association of (3H)MSO with intracellular particulate fractions. Since closely similar proportions of MSO occurred in the crude mitochondrial and the microsomal fractions, these fractions were analysed further: (a) (3H)MSO was bound to nerve endings sedimenting at the 1.0M to 1.2M sucrose interface; this binding was not abolished by prior increase in the endogenous cerebral methionine pool; and (b) (3H)MSO was released by subjecting the nerve endings to osmotic shock. However, the striking finding was that (3H)MSO could not be released from the nerve endings of the cerebellum from animals pretreated with methionine. (4) An association of (3H)MSO was observed with the membranes of the endoplasmic reticulum and specifically with its agranular component. (5) The results implicate the cerebellum as the primary target for MSO, in confirmation of the original observations of Lodin (1958). 41 references. (author abstract)

090149 Schwartz, A. S.; Eidelberg, E. Division of Neurobiology, Barrow Neurological Institute of St. Joseph's Hospital and Medical Center, Phoenix, Arizona Role of biogenic amines in morphine dependence in the rat. *Life Sciences.* 9(11):613-624, 1970.

The effect of depleting the rat brain of serotonin or catecholamines upon the precipitated abstinence symptoms in morphine - dependent rats were studied. Serotonin depletion by prior administration of p-chlorophenylalanine did not modify the symptoms of ptosis, diarrhea, number of 'wet dog' shakes or temperature change, whereas depletion of brain norepinephrine by d-1-alpha-methyl-p-tyrosine (AMPT) significantly reduced the number of shakes and the hypothermia precipitated by nalorphine. Administration of L-DOPA 3 hours before precipitating the abstinence syndrome prevented the amelioration of symptoms by AMPT. Modification of catecholamine metabolism by diethyldithiocarbamate and imipramine also reduced the shakes, but affected temperature changes variably. The complete expression of the abstinence syndrome in the rat appears to depend upon adequate brain levels of norepinephrine. 24 references. (author abstract)

090189 Frank, G. B.; Jhamandas, K. Department of Pharmacology, University of Alberta, Edmon-

ton, Alberta, Canada Effects of general stimulant drugs on the electrical responses of isolated slabs of cat's cerebral cortex. ***British Journal of Pharmacology (London).*** **39(4):716-723, 1970.**

The effects of some central stimulants on the electrical responses of isolated slabs of cat cerebral cortex were studied. In the neuronally isolated cortex of the cat, local application of bemegride, picrotoxin, nikethamide, caffeine and strychnine facilitated the surface positive response of the isolated cortex and lowered the stimulus threshold for this response. Excepting nikethamide, they all produced convulsive discharge in the isolated cortex unrelated to the applied stimulus. Local application of glutamate to the cortex produced spreading depression, which was sometimes preceded by spontaneous positive bursting. In contrast to the general depressants which produce a relatively consistent pattern of effects on the electrical responses of isolated cortex, the general stimulants, although they all have excitatory effects on isolated cortex, each produced a greatly different type of electrical response in the isolated cortex, suggesting that several different mechanisms of action are responsible for their effects. 6 references. (author abstract modified)

090355 Matlina, E. Sh.; Osipova, M. S. Laboratoriya po izucheniyu nervnykh i gumoral'nykh regulyatsiy imeni H. I. Grashchenkova Akademii Nauk SSSR, Moscow, U.S.S.R. /Influence of aminazin on adrenalin, noradrenalin, dopamine, and dopa excretion in healthy people and in the manic phase of the manic-depressive psychosis./ Vliyanie aminazina na ekskretsiyu adrenalina, noradrenalina, dofamina i DOFA u zdorovykh lyudey i pri manikal'noy faze manikal'no-depressivnogo psikhoza. ***Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Moskva).*** **70(1):128-131, 1970.**

Studies of epinephrine, norepinephrine, hydroxytyramine, and dihydroxyphenylalanine content in urine revealed that 3 hours after the administration of aminazine to healthy subjects, the excretion of epinephrine, hydroxytyramine and dihydroxyphenylalanine increased and the excretion of norepinephrine decreased. These changes can be conditioned by activation of the cortical layer of the suprarenals, inhibition of related norepinephrine from the adrenergic granules and absorption of it by the circulating blood. Aminazine may directly influence the stimulation of catecholamine biosynthesis. In granules during a manic phase of the manic - depressive psychosis, the influence of aminazine on the excretion of adrenergic substances is delayed; in such cases aminazine does not block norepinephrine in the adrenergical granules. 21 references. (author abstract modified)

090373 Cavanaugh, John H.; Griffith, John D.; Oates, John A. Division of Clinical Pharmacology, Abbott Laboratories, North Chicago, Illinois 60064 Effect of amphetamine on the pressor response to tyramine: formation of p-hydroxynorephedrine from amphetamine in man. ***Clinical Pharmacology and Therapeutics.*** **11(5):656-664, 1970.**

The effect of amphetamine on the pressor sensitivity to the indirectly acting amine, tyramine, and to norepinephrine was determined in 6 male patients with a history of amphetamine abuse. Acute intravenous administration of amphetamine increased the sensitivity to both tyramine and norepinephrine to 200 to 300 percent of control. In contrast, long term administration reduced the sensitivity to tyramine to 60 to 70 percent of control, while the sensitivity to norepinephrine was still enhanced. A likely explanation for the diminished response to the indirectly acting amine is depletion of norepinephrine. In this study it was demonstrated that human subjects metabolize 3H-amphetamine to p-hydroxynorephedrine, an amine known to displace norepinephrine from the neuron terminal. 31 references. (author abstract modified)

090419 Baer, Leslie; Kassir, Suham; Fieve, Ronald. Department of Internal Medicine, New York State Psychiatric Institute, 722 West 168th Street, New York, New York 10032 Lithium-induced changes in electrolyte balance and tissue electrolyte concentration. ***Psychopharmacologia (Berlin).*** **17(3):216-224, 1970.**

Lithium carbonate was administered chronically in low doses, 0.2mEq/day, to rats on constant sodium diets. The changes in external sodium and potassium balance and brain sodium and potassium concentration were compared to those of control animals. Changes in external sodium balance were in some respects similar to those observed in patients treated with lithium. During the 14 day periods of lithium administration, cumulative sodium excretion was always greater in the lithium treated rats, and brain sodium concentration was consistently decreased. The mechanisms responsi-

ble for these changes are discussed and related to a possible mechanism of action of lithium in manic-depressive disease. 25 references. (author abstract)

090422 Martin, W. R.; Eades, C. G. National Institute of Mental Health, Addiction Research Center, P. O. Box 2000, Lexington, Kentucky 40501 The action of tryptamine on the dog spinal cord and its relationship to the agonistic actions of LSD-like psychotogens. *Psychopharmacologia (Berlin).* 17(3):242-257, 1970.

In chronic spinal dogs, LSD, mescaline, psilocin, 2,5-dimethoxy -4-methylamphetamine, methysergide and tryptamine facilitated the flexor reflex evoked by tetanic electrical stimulation of the toe and induced the stepping reflex. These effects were antagonized by chlorpromazine and cyproheptadine, but not by phenoxybenzamine. Serotonin and 5-hydroxytryptophan also facilitated the flexor reflex and evoked the stepping reflex, but these effects were not antagonized by cyproheptadine. These findings suggest that the mode of action of several LSD-like psychotogens is similar to that of tryptamine and is different from that of serotonin or 5-hydroxytryptophan. 13 references. (author abstract)

090451 Smits, S. E.; Takemori, A. E. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206 Studies on the receptors involved in the action of the various agents in the phenylbenzoquinone analgesic assay in mice. *British Journal of Pharmacology (London).* 39(3):639-646, 1970.

Tolerance to the activity of several narcotic analgesics (morphine, levorphanol, and methadone) and several narcotic - antagonist analgesics (pentazocine, cyclazocine, and nalorphine) was studied in the mouse phenylbenzoquinone stretching test. Virtually complete tolerance was induced by chronic treatment with each of the narcotic agents, while no apparent tolerance was induced by the narcotic antagonists. In morphine tolerant mice there was a high degree of cross-tolerance to the effects of not only the other narcotic drugs but also to those of the narcotic antagonists, acetylsalicylic acid, and physostigmine. The effects of morphine and pentazocine were antagonized by naloxone but not by atropine, while the effects of physostigmine were antagonized by atropine but not by naloxone. Neither atropine nor naloxone antagonized the effect of acetylsalicylic acid. The results of the tolerance study suggest that there is a fundamental difference in the consequences of receptor interaction for the narcotic and the narcotic - antagonist analgesics. Morphine tolerant mice exhibit cross-tolerance nonspecifically. The selectivity of naloxone and atropine differentiates the narcotic and narcotic analgesics from the other two agents used in this analgesic test. 16 references. (author abstract)

092166 Leibowitz, Sarah Fryer. Rockefeller University, New York, New York 10021 Reciprocal hunger-regulating circuits involving alpha- and beta-adrenergic receptors located, respectively, in the ventromedial and lateral hypothalamus. *Proceedings of the National Academy of Sciences.* 67(2):1063-1070, 1970.

The injection of adrenergic and adrenolytic drugs directly into the brain through permanently implanted cannulas has yielded results showing that food consumption in the rat is regulated by a hypothalamic alpha-adrenergic hunger system and a hypothalamic beta-adrenergic satiety system. The rats' differential responses to alpha-adrenergic and beta-adrenergic drugs injected into different hypothalamic sites indicate the following: 1) the lateral hypothalamic feeding center contains beta receptors, the activation of which produces satiation, presumably by inhibition of the lateral feeding cells; 2) the ventromedial hypothalamic satiety center contains alpha receptors, the activation of which produces eating, presumably by inhibition of the ventromedial satiety cells; and 3) the mediolateral perifornical area of the hypothalamus contains both alpha and beta receptors, which lead to inhibition of the ventromedial or lateral hypothalamic centers respectively. It is suggested that the ventromedial and lateral hypothalamus are connected by reciprocal circuits, so that activation of the ventromedial center results in stimulation of the lateral beta receptors which inhibit the lateral feeding cells, and activation of the lateral center results in stimulation of the ventromedial alpha receptors which inhibit the ventromedial satiety cells. 11 references. (Author abstract)

092383 Gerwirtz, George P.; Kvetnansky, Richard; Weise, Virginia K.; Kopin, Irwin J. Laboratory of Clinical Science, NIMH, Bethesda, Maryland 20014 Effect of hypophysectomy on adrenal dopamine-beta-hydroxylase activity in the rat (Unpublished paper). Bethesda, Maryland, NIMH, 1970. 9 p.

Dopamine-beta-hydroxylase activity in the adrenal medulla is decreased one week after hypophysectomy. This activity can be restored by treatment with either ACTH or dexamethisone. Adrenal denervation also decreases adrenal dopamine-beta-hydroxylase activity and prevents elevation of this enzyme in response to immobilization. Intact pituitary adrenal and neuronal systems are required to maintain adrenal dopamine beta hydroxylase levels in nonimmobilized rats and to raise the levels in immobilized rats. 12 references. (Author abstract)

093132 Hoffer, B. J.; Siggins, G. R.; Oliver, A. P.; Bloom, F. E. Lab. of Neuropharmacology, Div. of Special Mental Health Research, NIMH, St. Elizabeths Hospital, Washington, D. C. 20032 Cyclic AMP mediation of norepinephrine inhibition in rat cerebellar cortex: a unique class of synaptic responses (Unpublished paper). Washington, D. C. NIMH, 1970. 36 p.

A unique class of synaptic responses has been demonstrated in studies of cyclic 3',5'-adenosine monophosphate (cyclic AMP) mediation of norepinephrine (NE) inhibition in rat cerebellar cortex. Evidence is presented for this inhibitory action and to suggest that the transmembrane responses to NE and cyclic AMP may indicate a unique and novel type of synaptic transmission. The extracellular recording techniques used on the rats are described. The modified multibarrel micropipette assemblies used in making intracellular recordings during microelectrophoretic testing in the comparison of the effects of NE and the cyclic nucleotides are described. The effects of NE and sympathomimetics on Purkinje cells, in particular the effects on mean spontaneous discharge rate and on interspike interval histograms, are discussed. The sympathomimetics -- epinephrine, isoproterenol, tyramine and amphetamines -- were evaluated for their effects on the discharge rate and pattern of cerebellar Purkinje cells. Mediation of NE responses by cyclic AMP, the effects of calcium and metal chelators, the effects of phosphodiesterase inhibitors, and the effects of prostaglandins and nicotinate were studied. An analysis is made of the transmembrane effects of NE and the cyclic nucleotides in Purkinje cells. The unique postsynaptic response to NE and cyclic nucleotides provides a model system for analysis of the widely distributed central catecholaminergic pathways. Moreover, endogenous self-regulatory synaptic agents, such as the prostaglandins add a new dimension of complexity to the functional control of the adrenergic synapses. Thus, the cerebellar cortex may be expected to provide further important clues to the understanding of cyclic AMP's functions in the central nervous system. 33 references.

094553 de Ropp, R. S.; Kastl, Lena; Matsuhiro, Betty. University of San Francisco, San Francisco, Calif. 94117 Study of amino acid analogs and brain biochemistry. Final Report, NIMH Grant MH-13687, 1970. 36 p.

Mood, activity, and other aspects of behavior have been associated with phases of amino acid metabolism in the central nervous system. A study of the effects of a variety of compounds on 2 enzyme systems is presented: the aromatic amino acid decarboxylases and the monoamine oxidases. Compounds which in any way modified enzyme kinetics in vitro, were tested for their effect on random activity in mice and on the conditioned fish. A program of organic synthesis was devoted to the synthesis of methoxy-substituted phenylalanines and phenethylamines to see whether there were relationships between position on the ring and modification of enzyme activity. The corresponding phenylpyruvic acids were also synthesized. It is difficult to make predictions about behavioral effects of compounds from the in vitro biochemical data on these enzyme systems. The strongest inhibitor of DOPA decarboxylase, 3,4-dihydroxycinnamic acid, had no effect on mouse behavior other than causing abdominal contractions whereas catechol, a moderate inhibitor of the enzyme, produced convulsions. The 2 compounds that were found tobe strong muscle relaxants, 3-isopropyl catechol and 4-tertiary butyl catechol, did not modify DOPA decarboxylase activity at all. The 2 compounds which caused nonenzymatic decarboxylation of DOPA in vitro had opposite effects in vivo: 4-tertiarybutyl catechol was a relaxant; 3,4-dihydroxytoluene was a convulsant. 7 references. (Author abstract modified)

095014 Barratt, Ernest S.; Russell, Glen; Creson, Daniel; Tupin, Joe. University of Texas Medical Branch, Galveston, Texas 77550 Neurophysiological and behavioral correlates of lithium. *Diseases of the Nervous System.* 31(5):335-337, 1970.

Summary is given of several investigations into the neurophysiological and behavioral correlates of lithium which are part of a larger research pro-

gram aimed at better describing the brain behavior correlates of 2 personality predispositions, impulsiveness and anxiety. During this research a 'motor set' theory of impulsiveness has been developed, and a neural system that provides a tentative neurophysiological basis for 'impulse control' has been outlined. Present research is aimed atidentifying drugs that differentially influence selected parts of this proposed neural system. Since manic patients often demonstrate 'impulse control' problems and since lithium carbonate appears to be an effective therapeutic agent in controlling manic disorders, an exploratory investigation of the concurrent effects of lithium on the functioning of selected nuclei within the brain and on behavior was undertaken. This research involved both acute and chronic experiments with lower animals and several psychophysiological experiments with normal human subjects. The acute cat studies suggest that the orbital frontal cortex is the site of the initial action of lithium. Chronic cat and monkey studies suggest a generalized slowing of the electroencephalograph through a wide range of neural centers after a 4 to 7 day buildup of lithium. Tissue studies suggest the frontal and temporal lobes as sites of greatest lithium concentration. An outline is given of ongoing experiments aimed at clarifying the discrepancies noted between the chronic and acute experiments. 2 references.

095351 Glick, S. D.; Jarvik, M. E.; Nakamura, R. K. Depts. of Pharmacology and Psychiatry, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, New York 10461 Inhibition by drugs of smoking behaviour in monkeys. ***Nature (London).*** **227(5261):969-971, 1970.**

Drugs that block nicotine action in cigarette smoke were administered to 4 rhesus monkeys who had been trained to puff on cigarettes. The drugs included mecamylamine, pentobarbitol, hexamethonium, scopolamine, and D-amphetamine. Results have only limited correlation to human smoking, mainly because of the difference between smoking modes of humans and monkeys. Nevertheless, the data show promise of inhibition of smoking by humans with the use of nicotine blocking drugs. 7 references.

095440 Schubert, Johan; Fyro, Bengt; Nyback, Henrik; Sedvall, Goran. Department of Psychiatry, St. Goran's Hospital, S-104 01 Stockholm 60, Sweden Effects of cocaine and amphetamine on the metabolism of tryptophan and 5-hydroxytryptamine in mouse brain in vivo. ***Journal of Pharmacy and Pharmacology (London).*** **22(11):860-862, 1970.**

The effects of cocaine and amphetamine on the metabolism of tryptophan and 5-hydroxytryptamine (5-HT) in the mouse brain are studied. The rates of accumulation and disappearance of 3H-5-HT in mouse brain in vivo, after administration of 3H-tryptophan have been determined. It was shown that cocaine and possibly also amphetamine reduced the accumulation of 3H-5-HT in brain in comparison to saline treated animals. No significant effect of the drugs on the contents of 3H-tryptophan, endogenous 5 HT or tryptophan was found after the relatively short period following drug administration. The rates of disappearance of 3H-tryptophan and 3H-5-HT were significantly retarded by both administered drugs. These results are discussed. 10 references.

095697 Hamilton, Leonard W. Department of Psychology, Rutgers University, New Brunswick, New Jersey 08903 Inhibitory functions of the septum and amygdala. Final Report, NIMH Grant MH-16441, 1970. 6 p.

The major achievements anticipated during the first year were to set up a laboratory and to begin to work on a long-term research program aimed toward a more detailed understanding of the anatomical and pharmacological bases of behavioral inhibition. The projects were undertaken to obtain a more detailed analysis of the disinhibitory effects observed following septal lesions or the administration of cholinergic locking agents. The results suggest that these manipulations produce complex changes in the organism's response to environmental stimuli. Although these changes are generally in the direction of a failure to inhibit responding, the specificity of some of these effects indicate that the inhibitory system is involved in very discrete modulation of responding. Other projects were undertaken to obtain a more detailed description of the anatomical structures involved in behavioral inhibition. The results indicate that the inhibitory system, like several other major functional systems, is rather diffusely represented throughout the limbic system. 4 references.

097548 Essig, C. F. U. S. Dept, H. E. W. Public Health Service, National Inst. of Mental Health, Clinical Research Center, Lexington, Kentucky Reduction of barbiturate dependence induced by

repeated electroconvulsions. *Archives Internationales de Pharmacodynamie et de Therapie (Ghent).* 188(2):387-391, 1970.

Observations have suggested that repeated electroconvulsions (EC) might enhance intrinsic brain mechanisms capable of resisting seizures of various origins. Thus the administration of repeated EC before rather than during sodium barbital (SB) withdrawal might result in some protection against barbiturate abstinence seizures. This hypothesis was tested with rats, and reduction of barbiturate dependence induced by repeated EC was demonstrated. Repeated EC were administered to rats that had been drinking SB. This was done to decrease or prevent the occurrence of barbiturate abstinence convulsions when the drug was discontinued. The administration of EC was associated with a significant reduction in the oral consumption of SB. Although physical dependence had probably developed the rats underwent a gradual withdrawal of the drug. 13 references. (Author abstract modified)

097958 Bhagat, B. Department of Physiology, St. Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis, Missouri 63104 Influence of chronic administration of nicotine on the turnover and metabolism of noradrenaline in the rat brain. *Psychopharmacologia (Berlin).* 18(4):325-332, 1970.

The influence of chronic administration of nicotine on the turnover and metabolism of noradrenaline in the rat brain is investigated. It was found that the administration of nicotine (0.5mg/kg.,subcutaneously, 3 to 5 times a day for 6 weeks) accelerated the rate of disappearance of introventricularly administered 3H-noradrenaline from rat brain. This was associated with normal levels of 3H-normetanephrine suggesting an increase in intraneuronal deamination. The rate constant of amine decline (k) in animals chronically treated with nicotine was significantlygreater than that of controls, while the steady state level of brain noradrenaline was about equal in both groups of rats. Amphetamine, reserpine, acetylcholine, histamine, pheniprazine, pargyline, and nicotine affected the catecholamine levels in the rat brain treated with nicotine to the same degree as they did in the controls. It is concluded that chronic administration of nicotine may increase noradrenaline turnover in the brain and possibly increase the deamination of this amine. 21 references. (Author abstract modified)

097962 Sigg, E. B.; Keim, K. L. Hoffmann-La Roche Inc., Nutley, New Jersey 07110 Enhancement by desipramine of hypothalamically evoked discharges in preganglionic sympathetic nerves. *Psychopharmacologia (Berlin).* 18(4):378-386, 1970.

Enhancement by desipramine of hypothalamically evoked discharges in preganglionic sympathetic nerves is demonstrated in cats. It has been previously demonstrated that chlorpromazine does not share in this action. Desipramine in intravenous doses of 0.3to 3mg/kg in the cat enhances preganglionic cervical sympathetic nerve activity evoked by hypothalamic stimulation. This effect is dependent on the pulsefrequency of stimulation. Spontaneous potentials are in general slightly diminished. Reflex excitation of preganglionic sympathetic outflow induced by sciatic nerve stimulation is not altered by desipramine. The described effects are interpreted as the result of a modulating influence of desipramine on central structures controlling ssympathetic outflow. 17 references. (Author abstract modified)

097988 Oxenkrug, G. F. Leningradskogo Nauchno-Issledovatel'skogo Psikhonevrologicheskogo Instituta IM. V. M. Bekhtereva, Leningrad, U.S.S.R. /Central antiserotoninergic effect of antimanic drugs./ Tsentral'nyy antiserotoninergicheskiy effekt antimaniakal'nykh preparatov. *In: Lapin, I., Serotoninergic Processes in the Action of Psych. Drugs.* **Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 68-76).**

The action of antimanic drugs on brain biogenic amines (especially on serotonin) was investigated. Haloperidol (0.1and 0.5mg/kg), lithium (10 and 100mg/kg), and BC-105 (0.5mg/kg) had no influence on brain serotonin in mice. Lithium (200mg/kg) lowered brain serotonin. Haloperidol (0.5mg/kg) and lithium (100mg/kg) diminished the 5-HTP produced elevation of brain serotonin. Haloperidol (0.1and 0.5mg/kg), and BC-105 (0.5mg/kg) but not lithium, lowered the brain noradrenaline. The possible role of inhibition of the central serotoninergic processes in the mechanism of the antimanic effect is discussed. 14 references. (Author abstract)

098003 Lapin, I. P. Laboratoriya Psikhofarmakologii Leningradskogo Nauchno-Issledovatel'skogo Psikhonevrologicheskogo Instituta IM. V. M. Bekhtereva, Leningrad /Role of brain serotonin in the stimulant action of amphetamine./

Uchastiye serotonina mozga v vozbuzhdayushchem deystvii fenamina. *In: Lapin, I., Serotoninergic processes in the action of psych. drugs.* Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 15-25).

An antiserotonin drug, the diethylamide of 2-bromolysergic acid (BOL-148, 1mg/kg) and a selective depletor of brain serotonin, p-chlorophenylalanine (200mg/kg given in 2 doses) prevented amphetamine produced stimulation of rearings, hyperthermia, and decreased group toxicity in mice. The precursor of serotonin, 5-hydroxytryptophan (10 to 60mg/kg) enhanced stimulant and hyperthermic effects of amphetamine. The stimulant action of amphetamine might be mediated through the release of brain serotonin and excitation of serotonin receptors. It is necessary to take into account the activation of central serotoninergic processes by amphetamine in the study of the interaction of various drugs with amphetamine. 14 references. (Author abstract)

098009 Samsonova, M. L. Laboratoriya Psikhofarmakologii Leningradskogo Nauchno-Issledovatel'skogo Psykhonevrologicheskogo Instituta IM. V. M. Bekhtereva, Leningrad /Excitatory effect of tryptophan in mice and rats and effect of imipramine and desmethylimipramine upon it./ Vozbuzhdayushchiy effekt triptofana na myshakh i vliyaniye na nego impiramina i demetilimipramina. *In: Lapin, I., Serotoninergic Processes in the Action of Psych. Drugs.* Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 103-112).

D1-tryptophan (TP), in doses of 300mg/kg and higher, like 5-hydroxy- tryptophan (5-HTP), induced phenomena of head twitching in mice and rats. Pretreatment with an inhibitor of monoamine oxidase phenelzine (20mg/kg, i.p.,1 hr before TP in mice and 2 hrs before TP in rats) enhanced this phenomenon. Serotonin blockers BOL-148 (1mg/kg) and deseril (1mg/kg), as well as an inhibitor of tryptophan hydroxylase, p-Chlorophenylalanine(300mg/kg) and an inhibitor of 5-HTP-decaboxylase, alpha-methyl dopa (300mg/kg), prevented TP produced head twitches in mice. These data suggest that TP produced head twitches result from the increase of the brain serotonin level. Imipramine (2 to 10mg/kg) potentiated and desmethylimipramine (1 to 25mg/kg) antagonized the described effect of TP. 11 references. (Author abstract)

098035 Shchelkunov, E. L. Laboratoriya Psikhofarmakologii Leningradskogo Nauchno-Issledovatel'skogo Instituta IM. V. M. Bekhtereva, Leningrad /On the analysis of 5-hydroxytryptophan produced hyperthermia in mice pretreated with a monoamine oxidase inhibitor niamid./ K analizu gipertermii, vyzyvayemoy 5-oksitriptofanom u myshey posle tormozheniya monoaminoksidazy niamidom. *In: Lapin, I., Serotoninergic Processes in the Action of Psych. Drugs.* Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 177-225).

The hyperthermic effect of 5-hydroxytryptophan (5-HTP; 20 to 150mg/kg) in mice pretreated with the monoamine oxidase (MAO) inhibitor niamid (20 to 100mg/kg) was studied. This hyperthermia is caused by serotonin (and not by 5-HTP itself) because it is prevented or delayed after inhibition of 5-HTP decarboxylase by NSD-1024 (50 to 100mg/kg) or by alpha-methyl-dihydroxyphenylalanine (250mg/kg). Hyperthermia is produced also by injection of 20 to 40mcg of serotonin or 5-HTP into lateral ventricules of the brain. Serotonin which does not penetrate sufficiently into the brain through the blood-brain barrier produces in higher doses (20 to 40mg/kg) under intraperitoneal or subcutaneous administration the drop of temperature which is increased and prolonged after the inhibition of MO0AO by niamid. Thus the hyperthermia produced by intraperitoneal or subcutaneous injection of 5-HTP after niamid is of central origin, probably in the peripheral localization of the adrenergic link (sympathetic nervous system). An attempt to use the hyperthermic effect of 5-HTP in niamid-pretreated mice to differentiate pharmacologically tricyclic antidepressants from anticholinergics was unsuccessful. At the same time it was possible to differentiate distinctly between antidepressants and anticholinergics. The fact that anticholinergics, like antidepressants, enhance the 5-HTP hyper- thermia illustrates the universality and significance of the principle of mutual counterbalancing of ergotropic and trophotropic systems with their neuromediator supply. 38 references. (Author abstract modified)

098040 Prakhye, I. B. Laboratoriya Psykhoframakologii Leningradskogo Nauchno-Issledovatel'skogo Psikhonevrologicheskogo Instituta IM. Bekhtereva, Leningrad /The influence of 5-hydroxytryptophan on the behavior and the level of monoamines in the brain of rats sensitive to sound./ Vliyaniye 5-oksitriptofana na uroven' monoaminov

mozga i povedeniye krys, chuvstvitel'nykh k zvuku. *In: Lapin, I., Serotoninergic Processes in the Action of Psych. Drugs.* Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 226-237).

The influence of the precursor of serotonin, 5-hydroxytryptophan (5-HTP), on audiogenic seizures was investigated. Effects of 5-HTP (hypothermia, head twitches) were compared in rats sensitive and nonsensitive to sound. Intraperitoneal injection of 5-HTP in doses of 200 and 250mg/kg weakened the seizures in 48% of the rats. 5-HTP in these doses lowered the quantity of head twitches in the nonsen- sitive ones. Hypothermic effect was the same in both groups of rats; 5-HTP in a dose of 250mg/kg produced death in 46% of the rats sensitive to sound on the next day after the injections and did not influence the control rats. The inhibitor of the synthesis of serotonin, p-chlorphenylalanine in a dose of 300mg/kg, increased audiogenic seizures in the rats sensitive to sound and did not influence the controls. Brain level of serotonin and norepinephrine was the same in audiogenic and intact rats. 5-HTP in doses of 200mg/kg produced an increase of serotonin in intact rats 16% greater in comparison to the audiogenic rats. 18 references. (Author abstract)

098042 Oksenkrug, G. F.; Osipova, S. V.; Uskova, N. V. Laboratoriya Psikhofarmakologii Leningradskogo Nauchno-Issledovatel'skogo Psikhonevrologicheskogo Instituta IM. V. M. Bekhtereva, Leningrad /Synergism of desmethylimipramine with reserpine and 5-hydroxytryptophan in the frog: brain serotonin and adrenaline and behavior./ Sinergism demetilimipramina s reserpinom i s 5-oksitriptofanom. Uroven' serotonina i adrenalina v mozgu lyagushek v sopostavlenii s izmeneniyami povedeniya. *In: Lapin, I., Serotoninergic processes in the action of psych. drugs.* Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 47-58).

The synergism of DMI (10mg/kg)with reserpine (10mg/kg), injected after phenelzine (25mg/kg), exists only if the level of brain sero- tonin is 3 times higher than in controls. DMI in combination with phenelzine and reserpine had no influence on the elevation of brain serotonin produced by these drugs. It is suggested that synergism of DMI with reserpine my be due to the central serotonin sensitizing action of DMI. Substance AW-151129 (10 and 20mg/kg) (imidazoquinazoline derivative) which acts on the adrinergic system without exhibiting any of the other activity component of the known antidepressants exerted no synergism with reserpine in the frog, in contrast to DMI. Hence, AW-151129 had no central srotonin positive action. The lack of thymoleptic effect of AW-151129 in depressive patients, which is associated with the absence of central serotonin positive effect confirms the hypothesis about the leading role of central serotonin-ergic processes in the thymoleptic effect. Fenfluramine (40mg/kg), which selectively releases the brain serotonin, produced the sedative effect and twitches of the extremities in frogs, but did not cause the lightening of the skin color. The lightening of skin color is not necessarily associated with the sedative action of reserpine. 12 references. (Author abstract modified)

098055 Lapin, I. P. Leninsgradskiy Nauchno-Issledovatel'skiy Psykhonevrologicheskiy Institut IM. V. M. Bekhtereva, Leningrad, U.S.S.R. /Serotoninergic processes in the action of psychotropic drugs./ Serotoninergicheskiye protsessy v deystvii psikhotropnykh sredstv. Leningrad, RSFSR Ministry of Health, 1970. 237 p. Vol. 53

Pharmacological and biochemical data are presented on the partic- ipation of brain serotonin in the action of the following drugs: amphetamine, a CNS stimulator; antidepressants, imipramine and desmethylimipramine; antimanics, lithium and haloperidol; and the tranquilizer phenigama. Experimental data is presented to show that antidipressants possess positive central serotonin action, whereas antimanics possess negative central serotonin action. The stimulant effect of amphetamine and anticholinergics is shown to be mediated through the release of brain serotonin. The second part of the volume is devoted to the pharmacological and biochemical effects of tryptophan and its metabolites 5-hydroxytryptophan and kynurenine. In general, the data reported show that serotoninergic processes play an important role in the action of psychotropic drugs.

098058 Azbekyan, S. G.; Oksenkrug, G. F. Laboratoriya Psikhofarmakologii Leningradskogo Nauchno-Issledovatel'skogo Psikhonevrologicheskogo Instituta IM. V. M. Bekhtereva, Leningrad /Serotoninergic component of the stimulant effect of cholinolytics./ Serotoninergicheskiy komponent stimuliruyushchego effekta kholinolitikov. *In: Lapin, I., Serotoninergic-*

processes in the action of psych. drugs. **Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 26-33).**

Benactyzine (10mg/kg), atropine (10mg/kg), and scopolamine (10mg/kg) stimulated both the vertical component of motor activity (rearings) and locomotion in mice. Benactyzine decreased brain serotonin level due to release of bound serotonin. There is a correlation between the stimulating action of benactyzine and the lowering of brain serotonin. Antagonists of serotonin BC-105 (0.5and 1.0mg/kg) and deseril (5mg/kg) prevented the effect of benactyzine on rearings, locomotion and brain serotonin. An inhibitot of serotonin synthesis, p-chlorphenylalanine (200 doses, 200mg/kg each), counteracted the stimulation of rearings produced by benactyzine and atropine. The possible role of the central serotoninergic processes in stimulant action of cholinolytics is discussed. 10 references. (Author abstract)

098064 Khaunina, R. A. Laboratoriya Psikhofarmakologii Leningradskogo Nauchno-Issledovatel'skogo Psikhonevrologicheskogo Instituta IM. V. M. Bekhtereva, Leningrad /On the analysis of the effects of 5-hydroxytryptophan./ K analizu effektov 5-oksitriptofana. *In: Lapin, I., Serotoninergic Processes in the Action of Psych. Drugs.* Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 139-149).

In experiments with mice, the 5-HTP effects on head twitches, hypothermia and diarrhea were investigated. Head twitches, induced by intraperitoneal injection of 5-HTP (250mg/kg) were depressed by an inhibitor of 5-HTP-decarboxylase, alpha-methyl-dopa (100mg/kg) and by serotoninolytic agents, BOL-148 (10mg/kg) and MCE (0.5mg/kg). Hypothermic action of 5-HTP was not diminished by alpha-methyl-dopa and serotoninolytic agents, whereas the latter weakened the hypothermic action of serotonin (25mg/kg I.P.). Thus, the hypothermia induced by 5-HTP may be provoked by the action of both 5-HTP proper and the serotonin formed from it. Alpha-methyl-dopa did not influence 5-HTP induced diarrhea. BOL-148 and MCE, in doses which completely sup- pressed the 5-HTP and serotonin induced head twitches, did not influence diarrhea. 10 references. (Author abstract)

098171 Buno, W., Jr.; Villar, J. I.; Tejerina, W.; Garcia-Austt, E. author address not given Effect of LSD-25, Chlorpromazine and Metedrine upon visual evoked response in cats. *Acta Neurologica Latinoamericana (Montevideo).* 16(1-4):64-73, 1970.

The actions of LSD-25, Metedrine and Chlorpromazine upon visual evoked responses (VER) recorded in different parts of the visual pathway, mesencephalic reticular formation and suprasylvian gyrus were studied in immobilized cats. Averages of the VER from these sites were obtained using a computer of averages transients while a drug was slowly and continuously injected. All the drugs produced a modification of the VER at different levels of the visual pathway. Some drugs also provoked changes in the ongoing electrocorticogram. No strict relationship was found between these 2 effects. The observed modifications appear to be specific and related to the concentration of drug injected, but are difficult to correlate to the effect of these drugs in man, particularly to their mode of action upon the nervous system. 10 references. (Journal abstract modified).

04 MECHANISM OF ACTION: BEHAVIORAL

089440 Barfknecht, C. F.; Miles, J. M.; Leseney, J. L. Division of Medicinal Chemistry, College of Pharmacy, University of Iowa, Iowa City, Iowa 522 1-(3,4-dimethoxyphenyl)-2-propanol effect on conditioned avoidance response in the rat. *Journal of Pharmaceutical Sciences.* 59(12):1842-1844, 1970.

The effect of 2-(3,4-dimethoxyphenyl)-2-propanol (DP) on conditioned avoidance response (CAR) in the rat is investigated. The compound, DP -- the oxygen analogue of the psychotominetic agent 3,4-dimethoxyamphetamine, was found to prolong latency times initially in a CAR test in rats. It was found to be a central nervous system depressant in mice. The structural implications of this action, plus the relationship between 1-(3,4-dimethoxyphenyl)-2-propanol and psychotomimetic amphetamines, are discussed. 6 references. (Author abstract modified)

089999 Benson, Herbert; Herd, J. Alan; Morse, W. H.; Kelleher, R. T. Department of Physiology, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts 02115 Hypotensive effects of chlordiazepoxide, amobarbital and chlorpromazine on behaviorally induced elevated arterial blood pressure in the squirrel monkey. *Journal of Pharmacology and Experimental Therapeutics.* 173(2):399-406, 1970.

Hypotensive and behavioral effects of chlordiazepoxide, amobarbital and chlorpromazine were studied in 5 unanesthetized squirrel monkeys whose mean arterial blood pressure had been increased by environmental means. Each monkey had been trained to press a key (respond) under a fixed ratio schedule of termination of a stimulus associated with noxious stimuli and had developed marked, persistent elevations of mean arterial blood pressure during the behavioral experiments. All three drugs decreased rates of response and mean blood pressure. 15 references. (author abstract modified)

090135 Weiss, Jay M.; McEwen, B. S.; Silva, M. T.; Kalbut, M. Rockefeller University, New York, New York 10021 Pituitary-adrenal alterations and fear responding. ***American Journal of Physiology.*** **218(3):864-868, 1970.**

The role of the pituitary - adrenal system in the regulation of fear motivated responses was studied in hypophysectomized and adrenalectomized rats. Hypophysectomized rats showed attenuated avoidance behavior in comparison to normal rats, while adrenalectomized rats showed more pronounced avoidance responding than normals. This was found using both passive and active avoidance, so that these effects could not be due to motor activity differences. Adrenocorticotrophic hormone enhanced the poor avoidance response of hypophysectomized animals and corticosterone reduced the supernormal responding of adrenalectomized animals. It is suggested that adrenocorticotrophic hormone increases excitability which leads to an increase in generalized fear or anxiety in fear situations, while corticosterone counteracts this influence because it acts to restore a normal level of excitability. 24 references.

090137 No author. Author address not given Experimental drug makes rats sexy. ***Medical World News.*** **11(4):20, 1970.**

Researchers at the National Heart and Lung Institute have found that an experimental compound, parachlorophenylalanine (PCPA) stimulates rats and rabbits. Sixty males were injected intraperitoneally with 100mg/kg of PCPA daily for 4 days and then were placed in cages in groups of 6 for observation. The animals began to mount each other and make copulatory movements as well as other signs of sexual stimulation. Of the 60 rats, 16 attempted at least one mounting during the 12 hour observation period, and 10 mounted 10 or more times. None of the 30 saline treated controls exhibited arousal. PCPA has also been used clinically by other NIH investigators to treat the carcinoid syndrome. Although the drug has been effective in lowering blood levels of serotonin and relieving severe gastrointestinal symptoms in most patients, no sexual excitation has occurred.

090157 Meldrum, B. S.; Naquet, R.; Balzano, E. Neuropsychiatric Research Unit, M. R. C., Carshalton, Surrey, England Effects of atropine and eserine on the electroencephalogram, on behaviour and on light-induced epilepsy in the adolescent baboon (Papio Papio). ***Electroencephalography and Clinical Neurophysiology (Amsterdam).*** **28:449-458, 1970.**

Conscious adolescent baboons (Papio papio) were given intravenous injections of atropine sulphate, atropine methylbromide or eserine sulfate and the effects on the EEG, on behavior, and on myoclonic responses to intermittent light stimulation (ILS) were observed. The classical alerting effects produced by eserine (0.2mg/kg) were maximal 5 to 10 min after injection and were accompanied by a sustained, high voltage fronto - Rolandic rhythm at 9 to 11 cycles/sec, resembling human mu rhythm in morphology and reactivity. After atropine (2 or 5mg/kg), periods of agitation and of sedation were seen. The sedation was most marked 20 to 60 min after injection. During this period an enhancement of EEG paroxysmal features was seen. Spikes and polyspikes and waves occurred predominantly in the fronto - Rolandic cortex, but also more diffusely. Beginning within 1 to 3 min of the injection of atropine and continuing for several hours, there was marked enhancement of the amplitude and frequency of lambda waves, which appeared in sustained bursts during the phases of agitation. Such sustained bursts of lambda waves were not seen after intravenous methylatropine (4mg/kg to 6mg/kg) or intraocular homatropine. After atropine (0.25mg/kg to 5.0mg/kg) and after eserine (0.05mg/kg to 0.3mg/kg), baboons with high, low or variable photosensitivity continued to display their characteristic responses to ILS when tested at the times of the maximal EEG drug effects. Neither drug made insensitive animals sensitive or led to ILS - induced seizures in photosensitive animals. It is concluded that the paroxysmal motor responses of baboons to ILS are not deter-

mined by the degree of activity in cholinergic nonspecific cortical afferent or corticocortical cholinergic systems. 27 references. (author abstract)

090418 Rosic, Nedeljko; Bignami, Giorgio. Laboratori di Chimica Terapeutica, Istituto Superiore di Sanita, Viale Regina Elena 299, I-00161 Rome, Italy Scopolamine effects on go-no go avoidance discriminations: influence of stimulus factors and primacy of training. *Psychopharmacologia (Berlin).* 17(3):203-215, 1970.

Rats were trained in a shuttlebox to perform 4 go-no go avoidance discrimination tasks, with various combinations of active and passive avoidance signals. The first task was learned with great average difficulty, and showed a large passive avoidance deficit after scopolamine treatment. Scopolamine exerted little or no effect on the performance of other tasks which were much easier to learn. After the completion of discrimination tests, active avoidance retraining was carried out with former passive avoidance cues. Retraining with noise as the conditioned stimulus (CS) showed identical acquisition rates in the groups which had previously performed with light as the active avoidance signal, and either noise or noise - light as the passive avoidance signal. Retraining with light as the CS showed faster acquisition in the former noise - go, light - no go group, as compared with the former noise -go, light and noise - no go group. An additional experiment showed that the elimination of active avoidance pretraining before discrimination training reduced the passive avoidance deficit and enhanced the active avoidance deficit provoked by scopolamine in the light - go, noise and light - no go task. The relative merits of various neuropsychological interpretations of the effects of central antimuscarinic agents are discussed. The role of built in hierarchies between stimulus - response relationships, and of response hierarchies are emphasized. 42 references. (author abstract modified)

090420 Schrold, J. Department of Pharmacology, A/S Ferrosan, Sydmarken 5, DK-2860 Soborg, Denmark Aggressive behaviour in chicks induced by tricyclic antidepressants. *Psychopharmacologia (Berlin).* 17(3):225-233, 1970.

The antidepressant drugs, imipramine, desipramine, protriptyline, nortriptyline, chlorimipramine and amitriptyline were administered to 3 to 10 day old chicks and changes in behavior were observed. Two pairs of chicks were used, one received the test drug and one received saline. The chicks were kept under constant observation for 2 to 4 hours. Aggressive behavior was defined as attack pecking by 1 chick directed against another. Normal chicks exhibited weak aggression. Among the treated chicks, aggressiveness always occurred together with hyperactivity. All 6 tricyclic antidepressants elicited a clear alteration of behavior. A few minutes after injection, the animals were tranquilized and showed decreased motor activity. This sedation ceased suddenly after 30 to 60 min and was replaced by excitation and aggressive behavior. Imipramine produced sedation only in the 4 to 6 week old fowl. No aggressive behavior was seen in young chicks with the use of imipramine. This was perhaps due to a marked decrease in the formation of normetanephrine in the chick brain. No clear cut difference was seen between the tertiary amines (chlorimipramine and imipramine) and the secondary amines (desipramine and nortriptyline). 20 references.

090421 Herman, Zbigniew S. Department of Pharmacology, Silesian School of Medicine, K. Marksa 38, Zabrze 8, Poland Studies on adrenergic mechanisms in the action of desmethyl imipramine (DMI). *Psychopharmacologia (Berlin).* 17(3):234-241, 1970.

The influence of alpha-methyl-tyrosine and diethyldithiocarbamate, which specifically inhibit noradrenalin synthesis, and the influence of p-chlorophenylalanine, which inhibits 5-hydroxytryptamine synthesis in the brain, on the antagonism between desmethylimipramine and 2-hydroxy-2-ethyl-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro -11-bH-benzoquinolizine (RO 4-1284) was studied in the rat. It was shown that both substances which inhibit noradrenaline synthesis, abolished the behavioral antagonism between desmethylimipramine and RO 4-1284. P-chlorophenylalanine was without effect on this antagonism. The evidence showed that desmethylimipramine antagonizes the action of a benzoquinolizine derivative by the participation of adrenergic mechanisms. 24 references. (author abstract)

090424 Bremner, F. J.; Cobb, H. W.; Hahn, W. C. Department of Psychology, Trinity University, San Antonio, Texas 78212 The effect of chlor-

diazepoxide on the behavior of rats in a conflict situation. *Psychopharmacologia (Berlin).* 17(3):275-282, 1970.

The effect of chlordiazepoxide on the behavior of rats in a conflict situation was studied. Two groups of rats (total of 29) were trained to press a lever when the cue was bright and not to press when the cue was dim. Lever presses when the lights were bright were rewarded by food pellets, whereas lever presses when the lights were dim were followed by electric shock. During a subsequent testing phase, the discrimination between bright and dim stimuli was made more difficult; and the experimental group was injected with chlordiazepoxide, 15mg/kg, while the control group received tap water, 1cc/kg. The chlordiazepoxide treated subjects made significantly more lever presses, spent less time on an escape platform, and discriminated better at the end of testing than the controls. These results were attributed to the reduction by chlordiazepoxide of the degree of suppression of lever pressing normally caused by response produced electric shock. 18 references. (author abstract)

090473 Coons, Edgar E.; Quartermain, David. New York University, New York, New York Motivational depression associated with norepinephrine-induced eating from the hypothalamus: resemblance to the ventromedial hyperphagic syndrome. *Physiology and Behavior (Oxford).* 5(6):687-692, 1970.

This study was done to show that norepinephrine injected rats behave in ways characteristic of ventromedially lesioned hyperphagic animals. Particularly that norepinephrine injected rats show motivational deficits in their willingness to work for food and, therefore, should perform better than saline injected rats on very easy tasks, while on difficult tasks they should perform more poorly. Fourteen rats with lateral hypothalamic cannulae were injected with norepinephrine and tested on appetitive tasks of varying difficulty when both hungry and satiated. On a simple consummatory test norepinephrine produced more eating than saline at both 0 and 24 hr of deprivation, and performance at 24 hr was more potentiated than that at 0 hr. On a continuously reinforced lever-pressing task, norepinephrine potentiated pressing only at 0 hr deprivation. When pressing was reinforced on a 30 sec variable interval schedule, norepinephrine potentiated pressing at 0 hr of deprivation, but after 24 hr of deprivation norepinephrine injected rats pressed significantly less than saline injected controls. It was found that norepinephrine seems to produce a motivational depression in a rat's willingness to work for food. The norepinephrine injected into theblood stream becomes vastly more diluted than that affecting the cells adjacent to the cannula in the brain. Thus, the fact that injecting the same dose by vein as by brain produced a complete cessation of lever pressing along with a violent autonomic reaction supports the notion advanced earlier that the amount of norepinephrine injected into the hypothalamus may be completely aphysiological in level. Thus, the effects observed following these brain injections may be the result of temporarily producing a functional lesion of neural tissue rather than stimulating it. The increase in eating but decrease in motivation to work for food after injections of norepinephrine is so similar to the effects of electrolytic lesions of the medial hypothalamic satiety system as to make such a hypothesis highly attractive for further research. 12 references. (author abstract modified)

091127 Fog, R.; Randrup, A.; Pakkenberg, H. Sct. Hans Hospital, Department E., DK-4000 Roskilde, Denmark Lesions in corpus striatum and cortex of rat brains and the effect on pharmacologically induced stereotyped, aggressive and cataleptic behaviour. *Psychopharmacologia (Berlin).* 18(4):346-356, 1970.

Extensive, controlled experiments investigating the role of the corpus striatum in amphetamine induced stereotypy are reported. In addition, experiments investigating the role of the corpus straitum in the development of other types of behavior such as rage reactions and catalepsy are reported. The results showed that large bilateral lesions affecting 30 to 90% of the corpus striatum inhibit stereotyped behavior in rats injected subcutaneously with amphetamine, but do not prevent rage reactions induced by injection of a monoamine oxidase inhibitor followed by injection of l-dopa. The stereotyped phase normally following this rage reaction is, however, absent in the operated rats. Small bilateral lesions in the corpus striatum (5 to 20%) cause a modified amphetamine stereotypy and prevent the usual cataleptic behavior produced by subcutaneous injection of a neuroleptic drug (perphenazine). Additional ablation of the overlying dorsal cortex

enhances these behavioral effects without qualitative changes. Both amphetamine and neuroleptics seem thus to mediate their behavioral effects through dopaminergic mechanisms in the corpus striatum. 32 references. (Author abstract modified)

091173 Hess, Eckhard H. University of Chicago, Chicago, Illinois The ethological approach to socialization. ***In: Early experiences and the process of socialization.*** **New York, Academic Press, 1970. (p. 19-36).**

The ethological approach to socialization is discussed. Social imprinting in chicks and ducks is a socialization process that is a form of learning that is genetically programmed. The process differs from the laws of association of learning in that imprinting occurs most efficiently during a specific sensitive period which lasts only during the first day of life; the first learned object rather than the most recently learned is the one learned most completely; the Law of Effect or spacing of trials does not improve the efficiency of learning; punishment enhances imprinting; imprinting is sensitive to carisoprodol and meprobamate; and the object to be learned is self-rewarding. Parental behavior in carrying out the socialization process is important for survival of the species. Smiling in babies and animal aggression are discussed with an ethological orientation. 28 references.

091997 Porsolt, Roger D.; Joyce, Daphne; Summerfield, Arthur. Department of Psychology, University College London, University of London, England Changes in behaviour with repeated testing under the influence of drugs: drug-experience interactions. ***Nature (London).*** **227(5255):286-287, 1970.**

Several pharmacological and behavioral factors were studied to assess their contributions to changes in rat behavior resulting from repeated testing in a Y-maze after injections of a mixture of 2 drugs. There was an increase in rat behavior in the Y-maze after injections of a mixture of 15mg/kg of amylobarbitone sodium and 0.75mg/kg of amphetamine sulphate, greater than the increase produced by any dose of either drug alone. Although the mixture contained a greater proportion by weight of barbiturate, it had similar effects to the combination used in a commercial preparation. When the procedure was repeated on the same rats over many days, there was a decline in hyperactivity, which stabilized at a much lower level after the first few tests. It is unlikely that this was due to tolerance to the pharmacological effects of the drugs after repeated administration. Behavioral habitation without the drug led to abolition of the drug response. No evidence was found that the decline in activity was a form of behavioral compensation, or combined tolerance to the drug and experience in the environment. 8 references.

092145 Hunt, Earl. University of Washington, Seattle, Washington Modification of learning by drugs; NIMH. Final Report, NIMH Grant, MH-13673, 1970. 7 p.

Studies on modification of learning by drugs have been made to provide further evidence concerning the mechanism by which analeptic drugs facilitate memory, and to provide data for the construction of mathematical models of memory which have a physiological basis. A brief summary of specific research results is given, with a view reporting overall progress instead of details. The effects of 2 dosage levels of pentelenetrazole on rats trained in a visual discrimination task facilitated learning, but timing depended on dosage. Having established satisfactorily the fact that if the electroconvulsive shock (ECS) is given immediately foolowing training (15 sec in the rat), a true retrograde amnesia will be produced, a study was made to determine if the ECS induced amnesia could be removed by injection of strychnine. Experiments supported the hypothesis that ECS interrupts the transfer of information from short term to long term memory (ECS induced amnesia is not apparent until the decay of short-term memory), and the effect of strychnine is evidently to remove the ECS prodiced block. The effect of the drug is to rearouse the animal's nervous system in some manner. The specificity of short-term and long-term memory in strains of mice was investigated but the specificity was not observed. 'Carry over' effect of pentelenetetrazole was investigated, in following a second side lead, but it was found unlikely that a 24 hour effect would occur at the doses customarily used in experimental studies of learning. Circuitry needed for passive avoidance studies was devised. 19 references.

092692 Iwahara, Shinkuro. Department of Psychology, Tokyo University of Education, Toyko, Japan 112 Interactions between the effects of chlordiazepoxide and amphetamine on food-intake and

spontaneous motor activity in the rat. ***Japanese Psychological Research (Tokyo).*** **12(2):82-86, 1970.**

The interactions between the effects of chlordiazepoxide (CDP) and amphetamine (AMPH) in food intake and spontaneous motor activity in the rat are investigated to determine if the interaction between the agents depends on the type of behavior affected. Drug combinations administered by injection were: saline (S)-S, CDP-S, S-AMPH and CDP-AMPH. The effects of the drugs on food intake were examined in the first experiment, and on motor activity in the second. The results showed that food intake was largest with CDP and least with AMPH. The CDP and AMPH combination yielded an almost identical amount of food consumption and that with S. Considerable interaction between the drug condition and the time sequence is shown. In the study of effects on motor activity, all paired comparisons of the means during the 1 hr period were significant at the 5%level except the one between S-AMPH and CDP and AMPH, although the latter sample means were always greater than the former. The depressant effect of CDP upon spontaneous activity was shown for only the first 20 min while AMPH increased activity throughout the 1 hr period, in comparison with saline controls. Of similar studies reported, the present one is probably the only one which indicates that the interaction between the effects of CDP and AMPH is different whether the effect is on food intake or motor activity. This finding is related to the hypothesis previously advanced that the CDP actions on food intake and motor activity are mediated by different underlying mechanisms. These mechanisms are discussed. 15 references.

095188 Tsai, Loh Seng; Perez, Vernon J.; Koonce, Jefferson M. California State College, Fullerton, California Effects of insulin, metrazol, and electroconvulsive shocks upon learning to learn 30 successive reversal problems by rats. ***Psychological Reports.*** **26(2):551-558, 1970.**

An enclosed T-maze was used, with water as incentive after 23 hours of deprivation to determine the relative effects of insulin, metrazol and electroconvulsive shocks upon learning to learn 30 successive reversal problems by rats. Each subject had to achieve 9 correct out of 10 daily trials before a problem was reversed. Forty adult male rats were equally divided into a control and 3 differently shocked groups. Shocks were administered on 3 alternate days followed by 2 days of rest. Each time, subjects of the 4 groups received respectively 0.5cc of saline, 55mg of metrazol per kg of body weight, 1 unit of insulin per 20 gm of body weight, and an electric current of 50 ma at 25 volts for 150 msec. Convulsion in the insulin group was prevented by an injection of dextrose and potassium chloride. The control was significantly superior to the 3 shocked groups which were remarkably similar or practically identical in their performance during the initial 6 problems. Thereafter, both nonconvulsive (saline and insulin) groups did better than the 2 convulsive groups either in terms of error, day, or 1 trial reversal score. 20 references. (author abstract modified)

095318 no author. author address not given Mayhem among the animals. ***World Medicine (London).*** **5(10):6, 1970.**

A research study involving rats found that the experimental compound parachlorophenylalanine (PCPA) induced sexual excitement. Brain amines revealed that PCPA lowered serotonin in male rats to about 10% of the concentrations in control animals, and norepinephrine to about 71% of control levels. The changes in sexual behavior produced by PCPA or PCPA-pargyline are attributed to the depletion of 5-hydroxytryptamine (5-HT) in the brain and the secondary unbalance between 5-HT and catecholamine activity. Since pargyline is a monamine oxidase inhibitor, the relative balance of serotoninergic and noradrenergic tone in the brain may control sexual behavior in male animals. Speculation about the compound's potential as an aphrodisiac for humans is still questionable. PCPA has, however, been used clinically to treat the carcinoid syndrome characterized by excessive production of serotonin and neurological diseases.

095671 Sheard, Michael H. Yale University School of Medicine, New Haven, Connecticut Effects of an acute stress of forebrain 5-hydroxytryptamine (5-HT) metabolism in C. N. S. lesioned and drug pretreated rats. Final Report, NIMH Grant MH-14687, 1970. 2 p.

Progress has been made in providing data to answer the following questons: what is the influence of the 5-hydroxytryptamine (5-HT) neuronal system on behavior and; how do the behavioral effects of drugs relate to this system? It has been possible to set up and equip a small laboratory for behavioral studies. Progress has ex-

tended into the areas: a study of single cell responses of the midbrain raphe region; studies on the effect of lithium on 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) and behavior; and studies on the effect of parachlorophenylalanine on behavior. Results include: stimulation of rats; stimulation of 5-HT midbrain raphe region causes increased threshold to painful stimulation; failure of habituation in rats on stimulation of midbrain raphe region is dependent on 5-HT; lithium induces an increased synthesis of 5-HT with increased production of 5-HIAA; P-chlorophenylalanine induces increased sexual and aggressive behavior in rats with lowering of 5-HT and 5-HIAA. Such behavior is counteracted by treatment with 5-hydroxytryptamine phosphate, which raises levels of 5-HT in the brain; a lowered threshold to LSD in midbrain raphe lesioned rats on FR schedule is noted. 8 references.

097952 McGaugh, James L.; Zornetzer, Steven F. Department of Psychobiology, School of Biological Sciences, University of California, Irvine, California 92664 Amnesia and brain seizures activity in mice: effects of diethyl ether anesthesia prior to electroshock stimulation. ***Communications in Behavioral Biology.*** **5(4):243-248, 1970.**

The amnesic effects of transcorneal electroschock stimulation in mice anesthetized with diethyl ether were examined. Deep ether anesthesia, but not light anesthesia, attenuated the amnesic effect of low current stimulation (15 ma, 200 msec). However, with high current (40 ma, 800 msec) deep ether anesthesia did not attenuate the amnesia. Electrocorticograms recorded from chronically implanted mice indicated that the brain seizure activity produced by electroshock stimulation is of shorter duration under deep ether anesthesia in comparison with those obtained with light anesthesia. These findings suggest that the degree of amnesia produced by electroshock stimulation depends upon alteration in processes that result in brain seizure activity. 17 references. (Author abstract)

097953 Squire, Larry R.; Geller, Anne; Jarvik, Murray E. Albert Einstein College of Medicine, Bronx, New York 10461 Habituation and activity as affected by cycloheximide. ***Communications in Behavioral Biology.*** **5(4):249-254, 1970.**

A study designed to explore the effect of protein synthesis inhibition on the development and retention of exploratory habituation is discussed. After mice were given subcutaneous injections of cycloheximide, which inhibits cerebral protein synthesis, their activity increased for 30 minutes and was then depressed. Habituation of exploratory activity following brief exposure to a novel area was retained for at least 14 days. Inhibition of protein synthesis initiated before or immediately following exposure had no effect on exploration during a subsequent session. These results are in contrast with previous results from passive avoidance training and discrimination tasks where cycloheximide exerted marked amnesic effects. 16 references. (Author abstract modified)

097959 Johnson, F. N. Department of Psychology, University of Birmingham, P. O. Box 363, Birmingham 15, England The effects of chlorpromazine on the expression of an acquired passive avoidance response in mice. ***Psychopharmacologia (Berlin).*** **18(4):333-345, 1970.**

The effects of chlorpromazine on the expression of an acquired passive avoidance response in mice is investigated. An apparatus for examining the retention and rate of extinction of 1 trial passive avoidance learning in mice is used in the studies to demonstrate first the effects of pretest administration of chlorpromazine and then to examine the permanence of these effects. Mice given 1 trial passive avoidance training were examined 24 hours later for retention of the acquired response. Testing was carried out with subjects given either chlorpromazine or saline injections before the test session. Three chlorpromazine doses (0.5, 2.0and 3.5mg/kg) were used, and 3 injection times (10, 90, or 180 min before testing). Chlorpromazine was found to impair the expression of the acquired response, both by depressing its initial elicitation and also by apparently facilitating extinction. A second experiment confirmed that extinction rate was indeed increased. A clear dosage effect was observed but injection time was not important in determining the drug's effect. Further experiments were undertaken to clarify the interpretation of the drug's action; in particular, the possibility that the effects might have been caused by a dissociation of learning between training and test situations was examined. It is suggested that the elevated extinction rates observed during testing when subjects were given chlorpromazine represents a temporary effect resulting from the reduced stimulus control of behavior. Permanent effects of pretest

drug administration were noted on the initial expression of the learned response. 24 references. (Author abstract modified)

097960 Svensson, Torgny H.; Waldeck, Bertil. Department of Pharmacology, University of Goteborg, Fack, Medicinaregatan, S-40033 Goteborg, Sweden On the role of brain catecholamines in motor activity: experiments with inhibitors of synthesis and of monoamine oxidase. *Psychopharmacologia (Berlin).* 18(4):357-365, 1970.

An investigation to further elucidate the possible causal relationship between catecholamine depletion and decrease in motor activity following administration of catecholamine synthesis inhibitors is undertaken. Amine depletion by these agents was prevented in the experiment by means of a monoamine oxidase (MAO) inhibitor, thus largely preventing a decrease in motor activity. Mice were pretreated with the MAO inhibitor, nialamide, and 16 hours later the dopamine (DA) beta-hydroxylase inhibitor, bis-(4-methl-1-homopiperazinylthiocarbonyl)- disulfide (FLA-63), or the tryosine hydroxylase inhibitor, alpha-methyltyrosine methylester (H44/68), was given. At different time intervals motor activity was measured and the brain levels of noradrenaline (NA) and DA were subsequently determined. Nialaminde increased both motor activity and amine levels. Chlorpromazine changed this hypermotility into a marked hypomotility. After FLA-63 the NA level was moderately reduced whereas DA remained high and motor activity was only slightly reduced. When H44/68 had been given both NA and DA levels were reduced while a definite reduction in motility could be observed. In these nialamine pretreated animals the synthesis inhibitors reduced catecholamine levels and motility much less than in normal animals. In separate experiments the degree of synthesis inhibition under the conditions described above was measured by estimation of the amount of 3H-DA and 3H-NA formed from 3H-tyrosine. It was concluded that both NA and DA are of importance in controlling motor activity. 24 references. (Author abstract modified)

097965 Appel, James B.; Lovell, Richard A.; Freedman, Daniel X. Psychopharmacology Laboratory, Department of Psychiatry, University of Chicago, Chicago, Illinois 60637 Alterations in the behavioral effects of LSD by pretreatment with p-chlorophenylalanine and alpha-methyl-p-tyrosine. *Psychopharmacologia (Berlin).* 18(4):387-406, 1970.

Alterations in the behavioral effects of lysergic acid diethylamide (LSD) by pretreatment with p-chlorophenylalanine (PCPA) and alpha-methyl-p-tyrosine (AMPT) are demonstrated in experiments with rats. The bar pressing behavior of hungry rats was maintained by a fixed ration schedule of food reinforcement. At 5 and 12 days after pretreatment with PCPA, a subthreshold dose (20 micrograms/kg) of LSD was found to disrupt this behavior. No such disruption occurred when PCPA pretreatment was followed by either a distracting external stimulus (tone) or a low dose of D-amphetamine (0.3mg/kg). Sensitivity to LSD was apparently unaffected by pretreatment with AMPT. 45 references. (Author abstract modified)

097989 Kiseleva, I. P. Laboratoriya Psikhofarmakologii Leningradskogo Nauchno-Issledovatel'skogo Psikhonevrologicheskogo Instituta IM. V. M. Bekhtereva, Leningrad /Inhibition of central serotoninergic excitation (5-hydroxytryptophan induced dead twitches) in mice by lithium./ Podavleniye litiyem tsentral'nogo serotoninergicheskogo vozbuzhdeniya u myshey (po fenomenu vstryakhivaniy golovy, byzvannykh 5-oksitriptofanum). *In: Lapin, I., Serotoninergic processes in the action of psych. drugs.* Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53. (p. 59-67).

Lithium carbonate suppressed 5-HTP induced head twitches in mice, i.e.,counteracted the central serotoninergic excitation, at a dosage of 100mg/kg, I.P. There was no inhibitory action of lithium on rearings (standing up reactions) and rotorod performance. Suppression of 5-HTP induced head twitches (convulsions) by lithium is not due to the non-specific anticonvulsive or antitremor action, since litium did not influence convulsions produced by corazol (70mg/kg) and tremor produced by oxotremorine (0.2mg/kg). Lithium was compared with other antimanic drugs haloperidol and phenigama and also with the antiserotonin com- pounds BOL-148 and deseril. All the drugs suppressed 5-HTP induced head twitches in mice; however, phenigama and haloperidol suppressed head twitches only in doses which exert inhibitory action on rearings and rotorod performance. Thus, the antiserotonin effect of lithium is more specific in comparison to that of haloperidol and phenigama. BOL-148 and deseril inhibited head twitches without any influence on rearings and rotorod performance. As distinct from the latter, lithium did not prevent peripheral effects of serotonin (hypothermia, diarrhea). Although the nature of the central (head

twitches) and the peripheral (hypothermia, diarrhea) effects is different, the data obtained suggest the selective central antiserotonin action of lithium. Antimanic properties of lithium may be related to its selective central anti- serotonin effect. 9 references. (Author abstract)

098024 Allikmets, L. Kh.; Vakhing, V. A. Tsentral'naya Meditsinskaya Nauchno-Issledovatel'skaya Laboratoriya i Kafedra Spikhiatrii Tartuskogo Universiteta, Tartu, E.S.S.R. /Influence of imipramine, benactyzine and promazine on the effects of intraamygdaloid injection of acetylcholine and serotonin./ Deystviye intraamigdalyarnogo vvedeniya imipramina, amizila i promazina na tsentral'nyye effekty atsetilkholina i serotonina. ***In: Lapin, I., Serotoninergic processes in the action of psych. drugs.*** **Leningrad, RSFSR Ministry of Health, 1970. 237 p. v. 53 (p. 34-46).**

In experiments on unanesthetized cats in a fee behavior situation it was ascertained that following behavioral effects of acetylcholine, intraamigdaloid injection of imipramine and benactyzine exerted the opposite effect. Imipramine inhibited and benactyzine potentiated the exploratory motor reaction elicited by acetylcholine. In the basolateral part of the amygdala imipramine intensified the inhibitory effect of serotonin on behavior and antagonized the activation of the exploratory motor reaction. In the dorsomedial amygdala, imipramine potentiated the behavioral activation and salivation elicited by serotonin. The role of central serotoninergic and cholinergic substrates in the antidepressive effect of tricyclic compounds is briefly discussed. 31 references. (Author abstract)

098049 Cannizzaro, G.; Gianguzza, M.; Provenzano, P. M. Istituto di Farmacologia dell'Universita di Palermo, Italy /Effect of arginine n-acetylasparaginate on different patterns of discrimination./ Influence de l'n-acetylasparaginate d'arginine sur des modeles differents de discrimination. ***Psihofarmakologija 2: Radovi Drugog Jugosl. Psihof. Simpozija -- 1969.*** **Zagreb, Medicenska Naklada, 1970. 441 p. (p. 35-44).**

The effect of arginine n-acetylasparaginate on animal behavior in terms of operant conditioning is presented. The study was concerned with its effect on learning of 2 types of discrimination, its effect on the learning of discrimination compared with aversion stimulus, and its effect on the ability to discriminate under the influence of a tranquilizer (diazepam). The experiment was carried out on white adult rats in a chamber which was totally devoid of visual stimulation and partially (80%) deprived of auditory stimulation. The animals were deprived of water for 24 to 36 hrs.,then introduced into a Skinner type box, where they were trained to press a lever for water. After the training period was completed, the rats were taught to discriminate between light and temporal stimuli. For the study of this discrimination, arginine n-acetylasparaginate was injected I.P. at a dose of 100mg/kg, 45 min. before the test. The study of the effect of arginine n-acetyl- asparaginate on changes in light discrimination, in the presence of a nexious stimulus, and due to diazepam was tested in rats who had reached a high level of training. The medication facilitated the learning of temporal discrimination, but in the case of light discrinimation, improve- ment was negative. The effect of diazepam, in the presennce of a noxious stimulus, was to increase the number of responses significantly when the animals were under the influence of arginine n-acetylasparaginate. 11 references.

05 TOXICOLOGY AND SIDE EFFECTS

089998 Van Woert, Melvin H. Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06510 Effect of phenothiazines on melanoma tyrosinase activity. ***Journal of Pharmacology and Experimental Therapeutics.*** **173(2):256-264, 1970.**

Chronic chlorpromazine (CPZ) administration was demonstrated to increase the tyrosinase activity in the B-16 melanoma in vivo. In vitro, .001 M CPZ produced a 2 fold increase in the B-16 melanoma tyrosinase and a 50%increase in Harding-Passey melanoma tyrosinase. Other phenothiazine compounds also activated melanoma tyrosinase. Substituents in position 2 in the phenothiazine ring showed the following order of potency for activating tyrosinase: CF3 greater than Cl greater than H. At position 10 of phenothiazine a piperazinoalkyl side chain was more effective in increasing tyrosinase activity than an aliphatic amine. The activation of melanoma tyrosinase by CPZ was greatest in the melanosomal fraction of the melanocyte. Digitonin or a nonionic detergent, Igepal CO-630, eliminated the increase in melanoma tyrosinase induced by CPZ. CPZ appears to increase melanoma tyrosinase activity by an indirect

mechanism, probably related to changes in melanosomal membrane permeability. CPZ did not activate mushroom tyrosinase, serum tyrosinase from melanoma bearing mice or rat adrenal tyrosine hydroxylase; inhibition of these soluble enzymes occurred in the presence of high concentrations of CPZ. CPZ also increased the incorporation of C14-dopa into the B-16 melanoma in vivo. 24 references. (author abstract)

090032 Coldwell, Blake B.; Wiberg, G. Stuart; Trenholm, H. Locksley. Research Laboratories, Food and Drug Directorate, Dept. of National Health and Welfare, Ottawa, Canada Some effects of ethanol on the toxicity and distribution of barbiturates in rats. *Canadian Journal of Physiology and Pharmacology (Ottawa).* 48(4):254-264, 1970.

The interaction of ethanol with amobarbital, barbital, pentobarbital, phenobarbital and thiopental was investigated at both the pharmacological and metabolic levels in rats. Induction time was shortened and sleeping time lengthened by the administration of ethanol with each of the 5 barbiturates, the effects being most pronounced with barbital and phenobarbital. Brain levels of barbital, phenobarbital, acetaldehyde and acetone were increased by ethanol. Rats given amobarbital, pentobarbital and thiopental had significantly higher brain and serum barbiturate levels at the time of regain of the righting reflex than was present in rats given these barbiturates with ethanol, indicating that the CNS depression was not dependent only on the concentration of barbiturate in the brain. The decay profiles of serum barbiturate concentrations was not altered by ethanol, and the barbiturates had no effect on the brain and blood ethanol levels. Phenobarbital depressed blood and brain acetaldehyde levels, but not the acetone levels, in ethanol - treated animals. Pentobarbital and thiopental, alone or with ethanol, had no effect on the blood acetaldehyde levels but increased the brain acetaldehyde levels in ethanol - treated animals. Pentobarbital had no effect on blood acetone or acetaldehyde levels but increased the brain levels of these compounds and, when administered with ethanol, decreased the brain acetone concentration. Thiopental increased the blood acetone level and when administered to ethanol - treated animals, decreased the brain acetone levels. 38 references. (author abstract)

094164 Olney, John W.; Ho, Oi-lan. Washington University School of Medicine, St. Louis, Missouri 63110 Brain damage in infant mice following oral intake of glutamate, aspartate or cysteine. *Nature (London).* 227(5258):609-611, 1970.

Experiments are described that demonstrate hypothalamic damage in infant mice following relatively low oral doses of glutamate, and which also show that orally administered aspartate and cysteine can induce retinal and hypothalamic damage. These 3 substances comprise a select group of amino acids that are neuroexcitatory and can depolarize nerve membranes. Contrary to reports from other researchers who used adult animals, these experiments with tube fed infant animals raise serious questions about the advisability of supplementing the human infant diet with monosodium glutamate (MSG), especially since it is common practice to wean human infants on foods that are rich in natural glutamates. Substantial quantities of MSG are added to other foods to enhance flavoring. It is necessary to establish if damage to the infant nervous system could follow from oral as well as parenteral administration of glutamate. 13 references.

06 METHODS DEVELOPMENT

089437 Van Tyle, W. K.; Burkman, A. M. Division of Pharmacology, College of Pharmacy, Ohio State University, Columbus, Ohio 43210 New method for assaying antiapomorphine activity in pigeons. *Journal of Pharmaceutical Sciences.* 59(12):1757-1759, 1970.

A new method for assaying antiapomorphine activity in pigeons is described. The method utilizes an electronic monitoring system which is capable of estimating and recording the intensity of the apomorphine induced pecking syndrome. The system was evaluated with regard to its ability to function as an attendant free assay instrument. Instrument responses were compared with responses derived from a visual recording technique which has been routinely used since 1960. The new monitoring system provides accurate and highly reliable estimates of the desired biological parameters. 11 references. (Author abstract modified)

090423 Krsiak, M.; Steinberg, Hannah; Stolerman, I. P. Institute of Pharmacology, Czechoslovak Academy of Sciences, Prague, Czechoslovakia Uses and limitations of photocell activity cages for as-

sessing effects of drugs. *Psychopharmacologia (Berlin).* 17(3):2580274, 1970.

The behavior of rats placed in a new environment was determined simultaneously by photocells and by direct observation. Predictably, a typical photocell activity cage did not measure a simple or homogeneous pattern of behavior even in undrugged animals. Two components of behavior, the number of walks across the cage and of rears onto the hind feet, were correlated with photocell counts, but grooming was not. Even this agreement between observation and automation broke down if dexamphetamine was given; the correlation between rears and photocell counts was reduced by graded doses of dexamphetamine and by dexamphetamine - amylobarbitone mixtures, and the stimulant effect of dexamphetamine on walks was greatly exaggerated by the photocells. Such discrepancies were much smaller with amylobarbitone alone. For the testing of drugs, the use of activity cages seems to be more limited than has sometimes been supposed. Complex changes of behavior are masked by the relatively crude photocell counts, but they may bedetected by standardized observation. Watching the animals might also help with the development of improved automatic devices. 41 references. (author abstract)

090425 Kapadia, A. J.; Barber, M. A.; Martin, A. E. Analytical Research Laboratories, A. H. Robins Co., Inc., Richmond, Virginia 23220 Quantitative determination of butaperazine by TLC. ***Journal of Pharmaceutical Sciences.*** **59(10):1476-1479, 1970.**

A method for the separation and determination of butaperazine in the presence of its degradation products is described. A sample is streaked onto a thin layer of silica gel G under a stream of nitrogen. The chromatogram is developed with isopropyl alcohol ammonia (1N) (4:1). The separated butaperazine is removed from the silica gel by elution with methanol and is determined quantitatively by UV spectroscopy. Details of the elution technique are described. Using the proposed method, quantitative recoveries are obtained from tablets and syrups. 21 references. (author abstract)

092999 Ries, James J. Section on Technical Development, National Institute of Mental Health, Bethesda, Maryland 20014 Total internal reflection light chamber (Unpublished paper). Bethesda, Maryland, NIMH, 1970. 1 p.

A simple and effective total internal reflection light chamber is described and illustrated. The chamber is useful in vitro experimentation on small pieces of isolated tissue when good visualization through a dissecting microscope is required, and is suitable for electrophysiological or pharmacological investigations of isolated nerve or muscle.

094789 Forrest, I.S.; Brookes, L. G.; Barth, R. Department of Psychiatry, Stanford University School of Medicine, Palo Alto, California Use of hepatic microsomes in the preparation of model drug metabolites. ***Proceedings of the Western Pharmacology Society.*** **13:1-4, 1970.**

A method for the use of hepatic microsomes in the preparation of model drug metabolites is described. Significant interspecies differences in the drug metabolizing pathways for chlorpromazine had been noted in vivo studies with mammals, and the use of hepatic microsomes of 14 species was tested as an alternate to in vivo metabolic studies. Procedures for the preparation of the microsomes and incubation of the microsomal fraction with tritiated chlorpromazine are described. Results of the metabolic studies with hepatic microsomes from sheep, dog, rabbit and guinea pig are presented. Identified metabolites include: chlorpromazine N-oxide, 7-hydroxychlorpromazine and 7-hydroxychlorpromazine sulfoxide. Deaminated metabolites were detected. Conversion to preparative thin layer chromatography, now in process, will aid in producing tritium labelled metabolites in desired quantities. The economic aspects of the microsomal method of producing metabolites, compared to in vivo techniques, indicate that the use of sheep liver microsomes has practical value. 8 references.

095507 Lewi, P. J.; Niemegeers, C. J. E.; Verbruggen, F. J.; Braet, W. W.; Van Riel, D. G.; Janssen, P. A. J. Department of Scientific Data Processing and Pharmacology, Janssen Pharmaceutical Research Laboratories, Beerse, Belgium Application of on-line computer procedures to experimental control and evaluation of the effects of drugs on operant behavior (Sidman shock-avoidance responding by rats). ***Archives Internationales de Pharmacodynamie et de Therapie (Belgium).*** **186(2):402-412, 1970.**

Procedures for operant behavior experiments on rats have been automated by means of an

IBM-1800 process control computer. The design and functional characteristics of the automated experiment are described. Special emphasis is laid on graphical presentation of experimental data and results. Automation by computer of pharmacological assays on operant behavior results in more flexible and faster procedures. 12 references. (Author abstract)

097964 Avivi, Amiel; Chari-Bitron, Aviva. Department of Biochemistry, Israel Institute for Biological Research, Ness-Ziona, Israel Estimation of low chlorpromazine concentrations by surfacing and sinking reaction of minnows (Gambusia affinis). ***Psychopharmacologia (Berlin).*** **18(4):407-411, 1970.**

Estimation of low chlorpromazine concentrations in aqueous solutions can be made by observing the surfacing and sinking reactions of minnows (Gambusia affinis), a species found suitable for this purpose. The surfacing and sinking reactions of the fish allow the determination of chlorpromazine down to concentrations of 0.1micrograms/ml. In a given volume of solution, neither sex nor number of the fish per tube have any effect on their response to low doses. A twentyfold augmentation in volume causes a twofold increase in sensitivity. The time elapsing, from the beginning of immersion until onset of surfacing, increases with decreasing drug concentration. Partial recovery from the drug is obtained after washing of fish with tap water. Adaptation occurs when the fish are immersed for more than 48 hours. 8 references. (Author abstract modified)

07 EARLY CLINICAL DRUG TRIALS

090078 Tornya, P. T. 13 Anglo Road, Campsie, N.S.W. 2194, Australia Problems of new drugs. *Medical Journal of Australia (Sydney).* 1(25):1266, 1970.

In the literature accompanying a recently released drug, Doxepin, a global evaluation consisted of less than 240 patients in 1 table and less than 120 in another. The data consists of unpublished private company trials, which do not allow independent evaluation. Extrapyramidal effects are stated not to occur with Doxepin, yet they are listed under side effects. The maximum recommended dose is 300mg, yet it is stated that up to 600mg may be required in some cases. In a suicidal attempt between 750 to 1000mg were ingested, resulting in a series of generalized convulsions. This is a very small safety margin, much smaller than that for diazepam, amitriptyline and chlordiazepoxide, the most frequently compared drugs. The information accompanying new drugs should be reliable and cover a large number of trials. 1 reference.

091500 Delay, J.; Lemperiere, T.; Feline, A. author address not given /Clinical tests of piridoxilate in psychiatric therapy./ Essais du piridoxilate en therapeutique psychiatrique. *Annales Medico-psychologiques (Paris).* 2(4):606-613, 1970.

The results of a clinical study of Piridoxilate in psychiatric therapy are discussed. Thirty five patients were treated by oral administration and injection. Improvement was claimed with dementias, Korsakoff syndrome, cerebral atrophies. In affective disturbances, subjective and objective improvement of depressive states appeared. Case data, including tolerance factors, are tabulated and discussed.

091715 Martin, William E. Dept. of Neurology, University of Minnesota Medical School, Minneapolis, Minn. L-dopa in the treatment of Parkinson's disease. *Postgraduate Medicine.* 47(6):153-157, 1970.

Several clinical trials involving the use of L-dopa in the treatment of Parkinson's disease are discussed, and use of the drug is evaluated. Reports confirm the necessity of administering large doses for extended periods, and while toxicity can be minimized by increasing the dosage slowly, control of symptoms may require a total dosage large enough to produce some form of toxicity. Psychologic abnormalities have been observed during most clinical trials. Such abnormalities include a feeling of total helplessness, hallucinations, depression, hypomania, and impaired sleep. If treatment with L-dopa is selected over other forms of therapy, caution must be exercised if the patient's history shows a major psychologic disorder, and careful supervision of the patient is mandatory. 21 references.

093090 Zucchi, Mario. Via Assarotti, 15/4, 16122 Genova, Italy /Pharmacological management of character-type behavior disturbances in the infant and child./ Osservazioni in merito alle attuali possibilita di trattamento farmacologico delle anomalie di comportamento di tipo caratteriale del bambino e del ragazzo. *Minerva Medica (Torino).* 61(82):4542-4550, 1970.

Observations are made on the pharmacological management of the character type of behavior disturbances in the infant and child. Treatment by a specialist is recommended in the management of serious cases of character disturbance, whereas average or less serious cases can be handled by the general practitioner or the pediatrician who is properly updated in psychopharmacology. The attention of specialists and the profession at large is drawn to a derivative of glutamic acid, (4-amino-3-hydroxybutyric acid), because of its ability to sedate the central nervous system without interfering with learning, concentration or memory processes. 25 references. (Journal abstract modified)

097971 Wilson, Roy D.; Traber, Daniel L.; Barratt, Ernest; Creson, Daniel L.; Schmitt, Richard C. Medical Branch, Texas University, Galveston, Texas Evaluation of CL-1848C: a new dissociative anesthetic in normal human volunteers. Springfield, Va., NTIS, AD-715484, 1970. 6 p. PC:$3.00 MF:$.95.

A multidiscipline comprehensive evaluation of a potentially useful new dissociative anesthetic agent was made in a group of normal human volunteers. The drug was found, in this study, to be psychologically acceptable, physiologically safe and apparently useful for the purpose intended and warrants further clinical investigation

in selected surgical patients. (Journal abstract - USGRDR)

097997 Ramsay,R. A.; Lehmann, H. E.; Ban, T. A.; Saxena, B. M.; Bennett, J. Douglas Hospital, 6875 LaSalle Bvd., Verdun, Quebec, Canada Clinical evaluation of a new psychotropic drug -- Molindone. *Int. Z. fur klinische Pharmakologie, Therapie und Toxikologie (Munchen).* 3(1):46-48, 1970.

A double-blind, controlled 12 week clinical study was performed to compare the therapeutic efficacy of Molindone to that of trifluoperazine in 20 patients with chronic schizophrenia. Molindone was found to be equal in its overall therapeutic effectiveness. While trifluoperazine was seen to be faster acting, Molindone produced in 3 patients a stim- ulation associated with euphoria. Data in animal experiments suggest further studies in chronically hospitalized psychotic patients with dysphoria or withdrawal manifestations. Adverse effects were minimal. 5 references. (Author abstract modified)

098172 Chouza, C.; Marin, C.; Romero, S.; Gomensoro, J. B. author address not given /Treatment of parkinsonism with L-Dopa./ Tratamiento del parkinsonismo con L-Dopa. *Acta Neurologica Latinoamericana (Montevideo).* 16(1-4):170-183, 1970.

Forty patients with Parkinson's disease were treated with L-Dopa over periods ranging from 1 1/2 to 7 months. The etiology of the condition was idiopathic in 29 patients, postencephalitic in 4, vascular in 2, following cyanide poisoning in 1 and doubtful in 4. No other antiparkinsonian medication was used on these patients. The rate of improvement was as high as 85%, including good, very good and excellent response to L-Dopa. Akinesia improved readily and spectacularly starting with a 2g daily dose, stiffness did so with doses over 2g daily but more markedly following 5g daily, while tremor, which regressed to an extent very much like the other symptoms, improved in general with doses of 4g daily or over. The improvements observed were independent of age, sex, etiology or severity of the clinical picture. On the other hand, there appeared to be a close relationship with course length, better results being observed in early cases of less than 5 years duration than in long dating cases. Particular attention is drawn to the case of parkinsonism following cyanide poisoning where there was a significant reduction of rigidity. Side effects occurred in all the patients but in only two instances was medication discontinued because of their intensity. Women patients exhibited a lower tolerance than men. Tolerance was improved with slow increases of the dose, splitting within each day and intake along with meals. Mild or intense pain was reported by 75%of the patients of varying localizations: polyartralgias, headache, sternochondral pain and diffuse pain. Hospitalization was not required in any of the cases, even with doses as high as 8g daily. 30 references. (Journal abstract modified).

100276 Deniker, Pierre. Faculty of Medicine of Paris, Paris, France Psychopharmacology: the role of clinical research. *In: Arieti, S., The world biennial of psychiatry and pyschotherapy.* New York, Basic Books, 1970. 622 p.(p.463-475).Vol.1.

Review of clinical research in psychopharmacology shows that it involves highly specialized effort that requires specially oriented institutes or research groups staffed with experienced personnel. Such units cannot be improvised; they must be fostered and their activity vigorously encouraged. The role of the clinic in such developments and discoveries as neuroleptics and tranquilizers, antidepressant drugs, and hallucinogens is discussed. Three stages of work in therapeutic tests are tests of tolerance, pilot or orientation studies, and extensive studies aimed at determination of the effects of a drug. These phases are described. Complete studies and controlled studies are discussed. 13 references.

08 DRUG TRIALS IN SCHIZOPHRENIA

089798 Corsico, Ruben; Chappa, Herbert Juan. Facultad de Ciencias Medicas, Universidad Nac. de La Plata, La Plata, Prov. de Buenos Aires, Argentina /The relationships between clinical and visomotor changes in a schizophrenic group./ Relaciones entre cambios clinicos y visomotores en un grupo de esquizofrenicos. *Acta Psiquiatrica y Psicologica de America Latina (Buenos Aires).* 16(4):350-353, 1970.

The relationships between clinical and visomotor changes in a schizophrenic group were measured before and after psychopharmacological treatment. Clinical changes were assessed by the Wittenborn rating psychiatric scale (EW) (1951) and a clinical remission scale (ERC). The Bender Gestalt test (BG) was used to assess visomotor changes, according to Pascal and Suttel

procedure. The pretreatment mean score was 184.4and 171.3the posttreatment score for the group. Prepost treatment differences were estimated by a variance analysis which reached a significant level for the EW. The scores for BG did not show any significant change after treatment; rank order correlation between EW and ERC showed a p equal to 0.62, for the posttreatment conditions. It is concluded that BG could be useful to detect psychotic conditions, but would be unable to assess changes in followup studies with psychotropic drugs of the type used here. 14 references. (Journal abstract)

090264 Megrabyan, A. A.; Melik-Pashayan, M. A. Yerevan, USSR /On the question of personality defects of consciousness in initial stages in schizophrenia./ K voprosu o defekte soznaniya lichnosti v iskhodnykh sostoyaniyakh pri shizofrenii. *In: Banshchikov, V., Problemy lichnosti.* Moscow, Akademii nauk SSSR, 1970. 423 p. (p. 404-411). Vol. 2.

A study of 23 schizophrenics with defective consciousness of the emotional - volitional type examines the possibility and degree of functional dynamic changes in their condition. A clinically homogeneous group of patients from 23 to 47 years of age, with schizophrenia for at least 10 years, was tested, before and after receiving 20mg of phenamine. A picture was projected for 30 seconds; the subject then closed his eyes and reported any afterimage. Simultaneous EEG measurements were made. In healthy control subjects, a depression of alpha rhythm was accompanied by several appearances of an afterimage. The majority of schizophrenics reported no afterimage, although a brief depression of alpha rhythm was recorded. After receiving phenamine, several reported distorted versions of the picture. Behavior changes are noted. The difference in visual afterimage before and after taking phenamine indicates functional - dynamic changes. It is concluded that desynchronization of alpha rhythm is an objective indication of a visual afterimage in the optic system which is not experienced by the patient consciously because of inadequate active attention.

091501 Ostaptzeff, G.; Ostaptzeff-Lavoine, M. author address not given /Observations on the neuroleptic syndrome./ A propos du syndrome neuroleptique. *Annales Medico-Psychologiques (Paris).* 2(4):614-617, 1970.

The secondary effects of using neuroleptic agents, expressed in the production of an extrapyramidal motor syndrome, are discussed. Two cases of schizophrenia treated by neuroleptics are reported. The secondary effects of these agents, the neuroleptic syndrome and its possible relations to extrapyramidal phenomena and to the antiparkinsonian agents used to correct the extrapyramidal effects are examined.

091502 Porot, Maurice; Couadau, A.; Plenat, M.; de Mori, V. Centre Hospitalier et Universitaire de Clermont-Ferrand, Hopital General, rue Sainte-Rose, F-63-Clermont-Ferrand, France /Clinical tests of thiothixene, neuroleptic disinhibiter./ Essais cliniques du thiothixene, neuroleptique desinhibiteur. *Annales Medico-Psychologiques (Paris).* 2(4):618-623, 1970.

Clinical tests of the neuroleptic disinhibitor, thiothixene, are discussed. Twenty patients, chiefly former schizophrenics were tested. In 7 cases, the results were excellent; in 7 others good; and in 6 cases mediocre or nul. Best results were obtained in the hebephenic -catatonic forms. Tolerance and comparison with other neuroleptics are discussed. (Author abstract modified)

093524 Jeri, F. R. Departamento de Neuropsiquiatria, Universidad Nacional Mayor de San Marcos, San Marcos, Peru /The use of haloperidol in residual schizophrenia and in paranoid states. El uso de haloperidol en la esquizofrenia residual y en los estados paranoides. *Revista de Neuro-Psiquiatria (Lima).* 33(2):114-122, 1970.

The odorless, colorless and tasteless haloperidol concentrate was given to 6 schizophrenic and 1 paranoid patient. Six of them would not take any antipsychotic medication or accept electricshock treatment. In 6 patients haloperidol produced a complete social remission. In 1 it failed to abort a relapse or eliminate troublesome halucinations.10 references. (Journal abstract)

096513 Skalnyy, V. V. Vol'nskaya Oblastiaya Psikhiatricheskaya Bol'nitsa, Volinsk, USSR /The effectiveness of simultaneous treatment with vitamine B12 and insulin in schizophrenic patients, according to the frequency of stable remissions./ Ob effektivnostilecheniya bol'nykh shizofreniyey vitaminom B12 odnovremenno s insulinom. *Zhurnal Nevropatologii i Psikhiatrii Imeni S. S. Korsakova (Moskva).* 70(11):1718-1721, 1970.

A clinicostatistical analysis demonstrated that in the use of small doses of insulin (8 to 15 units) in combination with vitamin B12 in schizophrenic patients with different forms (hallucinatory -- paranoid, simple, catatonic) the therapeutical effectivity is higher than in an ordinary insulin therapy. The results were assessed according to the frequency of remissions more than one year. In the hallucinatory paranoid form such remissions were more frequent (8.4%) than in a control group. In the paranoid form the percentage constituted in simple 13.7and in the catatonic 13.5%. (Journal abstract)

098002 Invernizzi, G.; Vitali, A. Universita degli studi di Milano, Istituto di Clinica Psichiatrica Istituti Ospedalieri di Milano, Milan, Italy /The combination of psychotropic drugs in the treatment of schizophrenia./ L'association des medicaments psychotropes dans la therapie de la schizophrenie. *Psihofarmakologija 2: Radovi Drugog Jugosl. Psihof. Simpozija -- 1969.* Zagreb, Medicenska Naklada, 1970. 441 p. (p. 175-180).

Pharmacologic therapy for schizophrenia has led to the development of new drugs but, in spite of the improvement in their efficacy, the drugs have shown only symptomatic relief. Thus, the use of several combined psychotropic drugs has been adopted. These combinations are of 2 kinds: the association of psychotropic drugs with parallel action; and association of psychotropic drugs with different actions. In some types of schizophrenia, chlorpromazine has a major effect on the symptoms of agitation, and haloperidol is effective in delirium, so that the therapeutic effect of the combined drugs is more marked than either one alone. With other types of schizophrenia, the tranquilizing drug may be associated with an antidepressive drug to produce a good effect. Chlorpromazine is given in doses of 300 to 400mg; haloperidol in doses of 3 to 5mg daily, and for the antidepressives: imipramine, 100 to 150mg, and amitryptiline, 75 to 100mg. For the catatonic schizophrenia, chlor- promazine (300 to 500mg) is combined with 3 to 5mg haloperidol, but the antidepressives are contraindicated. A table showing the superficial cell action and the deep cell action of different drugs is included, along with the site of action and mechanisms, and the histotlogical changes. 15 references.

098048 Kingstone, E.; Kolivakis, T.; Kossatz, I. Dept. of Psychiatry, McGill University, Montreal, Quebec, Canada Double blind study of clopenthixol and chlorpromazine in acute hospitalized schizophrenics. *Int. Z. fur klinische Pharmakologie, Therapie und Toxikologie (Munchen).* 3(1):41-45, 1970.

A double-blind study was performed on 41 patients, ages from 18 to 65 years, hospitalized with acute psychotic symptomatology. Twenty one patients received chlopromazine and the rest clopenthixol. Weekly evaluations showed no differences in the therapeutic efficacy of the 2 drugs; however, there were differences in the side effects. Drowsiness and extrapyramidal signs were more frequent with clopenthixol. Reactions affecting the skin appeared in 2 chlorpromazine patients. 11 references. (Author abstract modified)

100017 Gottfries, C.G. Ostra Sjukhuset, Mental Hospital of Malmo, 21224 Malmo, Sweden A double-blind investigation with flupenthixol and trifluoperazin at treatment of schizophrenic psychoses. *Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).* No.217:53, 1970.

Flupenthixol and trifluoperazin were compared in a double-blind crossover test on 85 schizophrenic patients. No obvious significant differences between the preparations could be established. The differences that did exist were positive towards flupenthixol. There was, during the first 3 months treatment period, a deterioration of the psychotic symptoms, which changed into an improvement during the second 3 months treatment period. During the first treatment period, there was an increase in patient activity which persisted through the second treatment period. The emotional reactions of the patients during the first treatment period were mostly unfavorable, but became more positive during the second treatment period. When earlier treatment (centrally inhibiting neuroleptic preparations) was discontinued and a transfer made to preparations with specific antipsychotic effect without central inhibition, an activation of psychosis symptoms, an increased activity, and increased anxiety symptoms in the patient resulted. If treatment is continued in connection with rehabilitation, the 'ostensible' deterioration is changed into an improvement. Between 25-35% of the patients had extrapyramidal symptoms. No other side effects were noted. Laboratory tests showed no changes that could be related to the treatment. Continued test with flupenthixol in the form of injections with depot preparations gave positive results. (Author abstract modified)

09 DRUG TRIALS IN AFFECTIVE DISORDERS

089787 Krulik, R.; Zvolsky, P. Psychiatry Dept., Medical School of Charles University, Prague 2, Ke Karlovu 11, Czechoslovakia The influence of lithium ion on the adrenocortical function of rats. ***Arzneimittel-Forschung (Aulendorf/Wurtt).*** **20(10):1577-1578, 1970.**

The influence of lithium, a substance used in the treatment of manic-depressive psychosis, on the metabolism of sugars is discussed. Specifically studied was the influence of the lithium ion on the adrenocortical function of rats. After the application of 2 mmol LiCl/kg/day to rats for 10 days no changes in the weight of adrenals and their contents of cholesterol were proved. The levels of corticosterone in the blood and urine had not changed either. After the application of 5 mmol/kg/day to rats for 10 days it was found that only the excretion of corticosterone had increased. The other indicators (the weight of adrenals, their contents of cholesterol and the level of corticosterone in the blood) had not changed. Evidence for the intervention of lithium in the metabolism of sugars by means of a change of adrenocortical function was not found. 12 references. (Author abstract modified)

091139 Masella, Cosimo. Instituto Psichiatrico 'San Lazzaro', Reggio Emilia, Italy /Prevention and treatment of hypotension by using psychopharmacology./ Prevenzione e trattamento dell'ipotensione da psicofarmaci. ***Rassegna di Studi Psichiatrici (Siena).*** **59(5-6):491-496, 1970.**

After having outlined the importance for the psychiatrist of the problem of hypotension due to psychotropic treatment, a report is made concerning 75 hospitalized female patients, treated with various psychotropic drugs, to which the administration of Dihydergot has been added. The last drug has been found to have a prolonged normotensive effect in a high percentage of cases, without the disadvantages formerly observed with other therapies, corrective of this secondary hypotension. 11 references. (Journal abstract)

092077 Mannironi, G.; Battistella, G. F. Ospedale Civile di La Spezia, Divisione di Neuropsichiatria, Italy /A study of dehydrobenzperydol (R 4749) in the treatment of dysthymic syndromes./ Sull'impiego del deidrobenzperidolo (R 4749) nel trattamento delle psicosi distimiche. ***Rassegna di Studi Psichiatrici (Siena).*** **59(3):219-237, 1970.**

Dehydrobenzperydol was used in the treatment of 21 hospitalized patients, affected mostly with manic or mixed dysthymic syndromes, given at an intramuscular or oral dosage of 4.0and 10.0mg/day (mean 6.37) for an average period of 21 days. The results were found to be positive in 82.0% of the cases. The patients were daily followed up according to rating scale target symptoms; dehydrobenzperydol was found to exert a relevant rapid effect on any excitement symptom (psychomotor agitation, clamorosity, impulsiveness, behavior disorders, insomnia, anxiety), on high mood (euphoria), deliria, hallucination, identification errors, and incoherence in ideation. It also has highly relevant efficacy on verbigeration and lalorrhea. These effects enable to ascribe to dehydrobenzperydol relevant properties of sedative and incisive neuroleptic agent. 8 references. (Journal abstract)

092688 Goodwin, Frederick K.; Murphy, Dennis L.; Bunney, William E., Jr. Section on Psychiatry, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014 L-dopa in depression (Unpublished paper). Bethesda, Maryland, NIMH, 1970. 16 p.

Results obtained on the use of sustained high doses of L-dopa in depressed patients are presented. Interests in the use of L-dopa in depression have arisen out of efforts to find a more direct way to evaluate the hypothesized role of cathecholamines in the pathogensis of affective illness. The catecholamine hypothesis of affective illness states that depression is associated with a functional deficit of brain neurotransmitter amine at specific central synapses, and that conversely mania is associated with a functional excess of these amines. All of the patients included in this study were classified as either manic-depressive or psychotic depressive. L-dopa and placebo were administered double-blind in a nonrandom design so that periods of drug and placebo were available for comparison within each patient. The overall results in 21 depressed patients are summarized. Only 25% of the total group (6 patients, 8 trial periods) showed a consistent improvement in depression on L-dopa. In 7 of the 8 trials in the responders, a relapse following placebo substitution was observed. It is of considerable interest that none of the clinical responses to L-dopa occurred among the agitated patients. This difference between the agitated and retarded groups in regard to L-dopa response is statistically significant. 43 references.

092975 Goodwin, Frederick K.; Murphy, Dennis L.; Brodie, Keith H.; Bunney, William E. Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland Levodopa: alterations in behavior. ***Clinical Pharmacology and Therapeutics.*** **12(2):383-396, 1970**

Results on the use of sustained high doses of levodopa in depressed patients are presented, and the psychiatric side effects encountered during the therapeutic use of the drug in Parkinson's disease are discussed against the background of the hypothesized role of catecholamines in the pathogenesis of affective disorders. One half of the patients were treated with smaller doses of levodopa in combination with a peripheral decarboxylase inhibitor (MK-485). Only 6 of 21 depressed patients consistently improved on levodopa, with relapse following placebo substitution and remission on restoration of the drug. A statistically significant increase in anger rating following 5 days of maximal dose of levodopa was noted as compared with that prior to treatment; others who previously experienced manic episodes manifested hypomanic behavior during treatment. Doses large enough to produce hypomania did not reverse depression. It is concluded that: 1) Amine depletion does not explain the pathophysiology of depression in most patients. 2) Hypomania occurs almost exclusively in affectively labile individuals. 3) The catecholamine hypothesis for depression may be an oversimplification in that mania and depression do not appear to represent the opposite poles of a single biochemical continuum. 4) Many factors contribute to psychiatric side effects – the predopa psychiatric state being the most important variable, levodopa often serving to unmask preexisting psychopathology. 38 references. (Author abstract)

093133 Sanarelli, L.; Rizzo, P. A.; Amabile, G. Clinica della Malattie Nervose e Mentali dell'Universita di Siena, Italy /Effects of nortriptyline in the treatment of depression syndromes./ Effetti della nortriptilina nel trattamento della sindromi depressive. ***Rassegna di Studi Psichiatrici (Siena).*** **59(5-6):507-513, 1970.**

The action of the nortriptyline in 43 depressed subjects was investigated; of these 18 were endogenous depressed, 19 neurotic depressed and 6 involutive depressed. The main action of the drug is displayed in the endogenous depressions. The effect is rapid with the usage of daily doses from 125 to 159mg. The treatment is well endured, lacking in secondary effects. 7 references. (Journal abstract)

093443 Rigotti, S.; Schergna, E.; Negrin, P. Clinica delle Malattie Nervose e Mentali dell'Universita di Padova, Padua, Italy /Clinical contribution of experiments with chlorimipramine (Anafranil)./ Contribution clinique a l'experimentation avec la chlorimipramine (Anafranil). ***Giornale di Psichiatria e di Neuropatologia (Ferrara).*** **98(1):79-86, 1970.**

Clinical experience with a new antidepressant drug, chlorimipramine is reported. The drug was given intravenously to depressed patients; chlorimipramine is the first antidepressant drug that can be administered by this route, and the qualitative reasons supporting this way of administration of the drug are discussed. The positive results obtained with chlorimipramine were similar to those already reported in the literature, and the collateral effects were rather mild. A clinical evaluation of the antidepressive effects of chlorimipramine is presented. 22 references. (Journal abstract)

094287 Yvonneau, M. Hopital Psychiatrique de Vauclaire, 24-Montpon-Menesterol, France /Lithium carbonate in psychiatric therapeutics./ Le carbonate de lithium en therapeutique psychiatrique. ***Evolution Psychiatrique (Toulouse).*** **35(11):407-429, 1970.**

The results of the clinical use of lithium carbonate in the control of manic excitations, chronic manias, and other cyclical states are discussed. Twenty six cases, including 13 manic-depressive psychoses (69% of favorable results), 4 involutional psychoses (0 favorable results), 2 atypical depressions (1 favorable result), 3 psychoptics with cyclothymia (2 favorable results), and 4 dementias with excitation (0 favorable results) were studied. The use of lithium carbonate with subjects who are physically fragile, and long treatment regimes, is not recommended. 43 references. (Journal abstract modified)

094307 Radmayr, E. A-6850 Dornbirn, Bahnhofsplatz, Germany /The problem patient in practice: contribution to a differential diagnostic problem of a type of depression./ Der Problempatient in der Praxis: Beitragzum differentialdiagnostischen und therapeutischen Problem der larvierten Depression. ***Medizinische Welt (Stuttgart).*** **21(48):2071-2077, 1970.**

The results of using the drug Sinquan in the treatment of certain psychiatric problem patients are discussed. Ambulant treatment with Sinquan was used on 500 patients suffering from depressive states. Symptoms were chiefly of the neurotic, phobic, organ neurotic, hypochondriacal and neurasthenic types. Sinquan proved to be an effective medication for this diagnostic group. 7 references. (Author abstract modified)

094453 Madalena, J. Caruso. Comissao Permanente para Assuntos Psiquiatricos do INPS, Brazil /Significance of psychopharmacology on psychotherapy of depression./ A significacao da psicofarmacologia na psicoterapia da depressao. *Revista de Psiquiatria (Rio de Janeiro).* 10(18):1-11, 1970.

How far psychopharmacology influenced psychotherapy is discussed. The concepts on depression (Sargant) have been thoroughly altered by psychochemotherapy. Depression, as related to the action of antidepressant agents, may be divided into 2 major groups: motivated depressions (reactive and situational -- Barahona Fernandes' psychological comprehensive mechanism); and caused depressions (endogenous and symptomatic or physical --Barahona Fernandes' psychobiological causal mechanism). The first group gets little or no result from chemotherapy, as its choice treatment is the psychotherapy. The second group, specially the endogenous depressions, may have its psychopathological structure fundamentally changed by chemical agents. Chemotherapy enabled the treatment of the stiff depression (with Frankl's 'drawing away' from psychosis) through psychotherapy, specially Frankl's logotherapy and Tellenbach's situational therapy. Disagreement with the controversial concept of bifocal treatment (Green, Racamier) is noted as it is believed that therapeutic data showed that chemotherapy psychotherapy synthesis is the best therapy for depression in its psychopathological and existential psychopathological aspects (Borgna). It is stressed that this treatment must be carried out by a 'pure' psychiatrist, free from any analytical extrapolation or neurophysiological absolutism. 20 references. (Journal abstract)

094963 Tolle, R. Universitats-Nervenklinik, 74 Tubingen, Osianderstrasse 22, Germany /Therapy of cyclothymia./ Therapie der Zyklothymie. *Deutsche Medizinische Wochenschrift (Stuttgart).* 95(45):2293-2295, 1970.

Medications and treatment regimens for the therapy of the cyclothymias are presented. Treatment indications and contraindications for the melancholic states and for the manic conditions are discussed. The melancholic states are treated largely with tricyclic antidepressants (thymoleptics). The treatment of manic states depends chiefly on the use of neuroleptics. Lithium salts are also effective with manic states, but are slower and perhaps better indicated as prophylactic agents. 4 references.

095013 Gershon, Samuel. Neuropsychopharmacology Research Unit, Department of Psychiatry, New York Univ. School of Medicine, 550 First Ave., New York, N. Y. 10016 Psychopharmacology of the lithium ion (twenty years after). *Diseases of the Nervous System.* 31(5):333-335, 1970.

Lithium occupies a unique and important position in modern psychopharmacology. Psychiatric use of lithium salts was impaired and delayed during early trials, particularly by indiscriminate use on patients taking low salt diets. Other aspects of the early history of lithium medication are briefly reviewed. Efficacy of the drug in treatment of manic phase, manic depressive disease and for prophylaxis of recurrent mania is discussed in relation to inconclusivenss of these and other claims. Biochemistry treatment and the use of lithium as a research tool are discussed, also. 15 references.

096512 Rumyantseva, G. M.; Fakrot, M. I.; Nefedyeva, M. I. Institut Psikhiatrii, AMN, Moscow, USSR /The use of lithium salts for the prevention of affective attacks./ Primeneniye soley litiya dlya profilaktiki affektivnykh pristupov. *Zhurnal Nevropatologii i Psikhiatrii Imeni S. S. Korsakova (Moskva).* 70(11):1712-1718, 1970.

The use of lithium carbonate in the treatment of 52 patients with affective disorders in schizophrenia, cyclothymia, and psychopathy is presented. It is concluded that lithium salts are an effective preparation for the prophylaxis of manic as well as depressive attacks. In its preventive action there are several stages. The first appears after 3 to 4 months of treatment and is characterized by a change in the clinical picture of the attacks. The second stage ensues after 6 to 7 months of treatment. The attacks become shorter, while the lucid periods become longer. The third stage ensues approximately after 1 year. This

stage is characterized by a decrease in the number of attacks or their full disappearance. During this treatment a control of the lithium content in the blood serum should be performed. A certain correlation between the preventive effect and the level of lithium in the blood serum of these patients is reported. 19 references. (Journal abstract)

097284 no author. author address not given Use of levodopa may be expanded by addition of MK485 to drug regimen. ***Journal of the American Medical Association.*** **212(11):1791-1792, 1970.**

A pilot study with depressed patients shows a reduction in peripheral side effect and potentation of the central nervous system activity when a hydrazine of a-methyl-dopa (MK485) is prescribed in combination with levodopa, which is administered in certain types of depression and in Parkinson's disease. A study conducted among 10 patients hospitalized for moderately severe to severe depression showed 4 patients improved on combined administration of these drugs. One patient with a history of mania became manic. This reaction, and previous experience with levodopa administered alone, indicate that the drug is contraindicated in patients with manic, or bipolar, depression. Reasons for the lack of response in the majority of patients are discussed, as are the results of other research studies using both drugs with other types of depressed patients.

097562 Kay, D. W. K.; Fahy, Thomas; Garside, R. F. University of Newcastle, Newcastle upon Tyne, NE1 4LP England A seventh-month double-blind trial of amitriptyline and diazepam in ECT-treated depressed patients. ***British Journal of Psychiatry (London).*** **117(541):667-671, 1970.**

A double blind trial designed to test the efficacy of amitriptyline over a 7 month period in 132 depressed patients treated with electroconvulsive therapy (ECT) is discussed. A control group selected at random was given diazepam. Both drugs were given the commencement of ECT. In patients remaining on the drug at 1 month there as a significant advantage to the amitriptyline group on 2 of the 4 rating scales used. During the remainder of the trial fewer patients in this group committed suicide, had further ECT, or failed to improve. Side effects, however, were more troublesome. A possible depressant effect of diazepam is considered. The importance of maintenance therapy and of adequate supervision in the after care of ECT treated depressive patients is indicated by the occurrence of 3 suicides in the group not receiving the antidepressant drug. 12 references. (Author abstract)

098018 Villeneuve, A.; Bourassa, G. Division de Recherches, Hopital St-Michel-Archange, Quebec, Canada /Lithium in psychiatry: clinical and biochemical aspects./ Le lithium en psychiatrie: aspects cliniques et biochimiques. ***Int. Z. fur klinische Pharmakologie, Therapie und Toxikologie (Munchen).*** **3(1):34-40, 1970.**

Lithium treatment in the form of carbonate was applied to 2 male and 9 female patients, age 32 to 56 years, with manic-depressive psychoses. Good therapeutic results were observed with manic episodes; the treatment also acted as a prophylaxis against the recurrence of manic and depres-sive states. Etiological studies on the modification of the metabolism of biogenic amines in connection with mental disease point to a catalytic action of lithium, particularly in controlling the noradrenaline level. Concerning its psychotropic action, it can be classified as a psycho- leptic, yet may not be regarded as a neuroleptic agent. Side effects were not observed at the dosage given. 48 references. (Author abstract modified)

100019 Kirk, L.; Gram, L.F.; Jensen, P.S. St.Hans Hospital, Department D, 4000 Roskilde, Denmark Clinical experience with 10mg reserpin injected i.m.in depressive disorders. ***Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).*** **No.217:55-56, 1970.**

Reserpine administered in treatment of hypertension produces severe depression as a side effect. All thymoleptic drugs reveal reserpine antagonism in pharmacological tests. Some cases have been reported of dramatic improvement after reserpine was given to depressive patients resistant to thymoleptics. Eight schizophrenic patients and 24 patients with depressive disorders have been treated with injection of 10mg reserpine intramuscularly. In 2 schizophrenic patients there was a slight but not impressive improvement. Among the depressive patients observed after a single dose: 2 patients became worse; 10 patients showed no change; 9 patients showed slight or transistent improvement; and 3 patients showed dramatic improvement. Under this treatment given 2 or 3 times weekly 4 of 8 patients showed a response much like ECT with gradual improvement. Typical manic-depressives improved better after pretreatment with thymoleptic

drugs. This was not necessary for the atypical or doubtful manicadepressive patients. Hypotension as side effect was not severe, and was easy to manage with elevation of the legs. Some patients became drowsy, others became excited. After 1 to 3 hours flushing of the face was seen in many patients. One patient with previous duodenal ulcer developed intestinal bleeding. Preliminary indications for reserpine treatment are: a) endogenous depression after treatment with thymoleptic without improvement; b) atypical depressive states with anxiety; c) in depressive stupor. If there is a slight or transistent improvement after one or two injections then the patients should continue with 2 or 3 treatments weekly. (Journal abstract modified)

100076 Baastrup, Poul Christian. State Hospital, 2600 Glostrup, Denmark Clinical problems in connection with the application of lithium. ***Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).*** **No.217:27, 1970.**

The lithium level in the organism is determined by the lithium intake and the renal elimination of lithium. It is therefore better to base the dosage on the patients' renal lithium clearance than on their body weight. Final adjustment of the maintenance dosage must, however, be based on each patient's response; there is a certain individual variation as regards the serum lithium concentrations necessary for full clinical effects and the concentration leading to side effects. The benefits derived from lithium therapy depend on the clinical picture of the patient; certain disorders and personality types seem particularly susceptible to the stabilizing action of lithium. (Journal abstract)

100082 Schou, Mogens; Baastrup, Poul Christian; Amdisen, A.; Poulsen, J.C.; Thomsen, K. Psychopharmacological Research Unit, Arhus State Hospital, 8240 Risskov, Denmark Concerning the evidence for a prophylactic action of lithium. ***Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).*** **No.217:27, 1970.**

Non-blind studies on lithium prophylaxis in recurrent endogenous affective disorders have now been supplemented by double-blind comparisons of lithium and placebo in matched patient groups; recurrent manic-depressive disorder and recurrent depressive disorder have been examined separately. The data serve to classify not only the question of lithium prophylaxis but also the role played by placebo effects and by the selection of patients. (Journal abstract)

10 DRUG TRIALS IN NEUROSES

089444 Rossman, M.; Moskowitz, M.; Fleishman, P.; Sheppard, Charles; Merlis, Sidney. Research Division, Central Islip State Hospital, Central Islip, New York The anti-anxiety effects of haloperidol and trifluoperazine in an outpatient neurotic population. ***Clinical and Basic Research.*** **31(11):130-133, 1970.**

The antianxiety effects of haloperidol and trifluoperazine were surveyed in a sample of 57 neurotic outpatients. Medication was prescribed double-blind to a maximum of 1.50mg of haloperidol and 2.75mg of trifluoperazine daily for an average duration of 30 days. The profiles of unwanted effects with regard to type and frequency and the attrition rate was different for each treatment form. While both drugs appear to be effective, no clear statement of superior efficacy can be drawn from the present data. (Author abstract)

091110 Pisani, D.; Nigro, A. Clinica delle Malattie Nervose e Mentali, dell'Universita di Messina, Italy /Pharmacological deconditioning./ Decondizionamento aspecifico farmacologico. ***Rivista di Neurobiologia (Arezzo).*** **16(3):329-336, 1970.**

A new neurophysiological theory has been proposed on the pathogenesis of psychoneurosis. It is emphasized that a state of fusal ipercontrol of muscular activity. On this basis it puts forth the proposal of deconditioning of psychoneurosis by pharmacological action. 5 references. (Author abstract)

092917 Knopp, Walter. author address not given Psychiatric changes in patients treated with levodopa: I. the clinical experiment. ***Neurology.*** **20(12):23-30, 1970.**

The case studies of 2 parkinsonian patients treated simultaneously by levodopa in the Clinical Research Center are reported. Similarities and differences in their clinical responses are pointed out and discussed in reference to psychosocial and psychiatric aspects of the study. The relationships between levodopa treatment and changes in neurological function; psychological rating scales; pupillary responses to light; handwriting size; catecholamine, indolamine, and electrolyte excretion patterns; urine osmolarity; and sleep electroencephalography were investigated. 17 references. (Author abstract modified)

093091 Bergamini, L.; Morgando, E.; Vurchio, A. M. Clinica delle Malattie Nervose e Mentali dell'Universita, 10100 Torino, Italy /Clinical experience with Anafranil./ Nostre esperienze cliniche con Anafranil. *Minerva Medica (Torino).* 61(82):4527-4531, 1970.

Clinical experiences with Anafranil are reported. Eighty eight cases of psychological depression with various symptom pictures received 25 to 100mg/day of Anafranil, an antidepressant, by intravenous or oral administration. The drug was found to be effective against both the nucleus of depression (endogenous and involutive forms) and against its anxiety component. Satisfactory results were obtained in 80% of the cases. 4 references. (Journal abstract modified)

098174 Querol, Mariano. Universidad Peruana Cayetano Heredia, Casilla 5045, Lima, Peru /Double blind study with antidepressants./ Estudio double ciego con antidepresivos. *Revista de Neuro-psiquiatria (Lima).* 33(4):251-270, 1970.

A double blind study was conducted to compare the actions of doxepine with those of amitriptyline in a random sample of 63 years. All but one of the subjects were outpatients. The frequency of depression type was: endogenous 30%, psychogenic 48%, other types 22%. The experiment lasted 4 weeks and subjective clinical controls and Hamilton's anxiety and depression rating scales were used. Daily doses of both drugs ranged from 25 to 150mg. Side effects were found to be insignificant. Doxepine was as effective or more effective than amitriptyline in treating any type of depressive syndrome, particularly because of its fast acting therapeutic effect. Both drugs had a powerful tranquilizing effect. 19 references. (Journal abstract modified)

11 DRUG TRIALS IN MISCELLANEOUS DIAGNOSTIC GROUPS

090188 Goodwin, F. K.; Brodie, H. K. H. Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland L-dopa with MK 485 for depression. *Lancet (London).* No. 7660:1339, 1970.

In answer to questions raised by a paper (Goodwin, F. K.;Brodie, H. K. H.;Murphy, D. L.;Bunney, W. E.;Lancet, May 2, 1970, p.908) on the combined use of L-dopa and a peripheral decarboxylase inhibitor in depression, the following points were clarified: (1) Placebo periods (involving the same number of capsules, but without MK 485 or dopa) preceded MK 485 - dopa combination in all patients. The initial placebo periods and the combination treatment period were from 2 to 5 weeks in duration. (2) Because the inherent tendency for spontaneous remission and exacerbation in affective illness must be considered in the design and interpretation of drug studies the protocols involved alternating drug and placebo periods. (3) The sample size was too small to substantiate any general therapeutic claim for the combination of MK 485 and dopa in depression. Rather, the central point of the study was that alpha-methyldopa hydrazine appears to be a safe drug capable of inhibiting the peripheral decarboxylation of administered L-dopa. Consequent reduction in the incidence of peripherally based side-effects may allow more rapid attainment of therapeutic levels, and a potentiation of the effects of L-dopa. 2 references.

090349 Shmilovich, L. A.; Polyak, A. I. Kishinevskaya respublikanskaya psikhiatricheskaya bol'nitsa No. 1, Kishinev, U.S.S.R. /Arresting of status epilepticus and serial seizures by amytal-caffeine./ Kupirovaniye epilepticheskogo statusa i seriynykh pripadkov amital-kofeinom. *Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Moskva).* 70(1):125-127, 1970.

In a clinical study of 50 patients, amytal-caffeine treatment successfully arrested serial seizures and status epilepticus. Where urgent measures are necessary, modifications of a combination of barbiturates with caffeine, adapted to the conditions of epileptic seizures are proposed. The study contains recommendations for the practical use of the indicated method. 16 references. (author abstract modified)

091076 Bieder, J. Hopital Psychiatrique de Bailleul, France /Indications for inhibitory medications./ Implications des medications-retard. *Annales Medico-Psychologiques (Paris).* 2(3):424-427, 1970.

A negative criticism is directed at extending the use of neuroleptic inhibitors to the treatment of alcoholics, delinquents, and paranoics. The utility of the inhibitors is uncertain and perhaps exaggerated. Indications for their use need further examination and discussion. A conservative attitude should be taken toward the newer inhibiting medications; they may be less effective and more ex-

pensive than their more ordinary homologues. 5 references.

091503 Gorceix, A.; Jacquemin, C. author address not given /Effect of pyrovalerone in the ambulatory treatment of fatigue states./ Interet du pyrovalerone dans le traitement ambulatoire des etats de fatigue. *Annales Medico-Psychologiques (Paris).* 2(4):624-632, 1970.

Clinical tests of the effects of pyrovalerone in the ambulatory treatment of fatigue states are discussed. The agent proved effective in organic and functional psychoses. It showed excellent tolerance and lack of secondary effects. Indications for further use must be subject to broader research.

091919 Jenkins, Ramon B.; Groh, Robert H. Washington, D.C. Psychic effects in patients treated with levodopa. *Journal of the American Medical Association.* 212(13):2265, 1970.

Physicians discuss clinical experience with psychic effects in 75 emotionally disturbed patients they treated with levodopa. These data are correlated to reports by others of aggravation of psychiatric symptoms following administration of levodopa to schizophrenic patients suffering from drug - induced parkinsonism, and the appearance of psychiatric symptoms in patients with Parkinson's disease. About 25% of the 75 patients were demented to some degree, and others had complained of poor memory. Results from these and other patients are summarized and 3 case histories, 2 of them aged patients, are given. Much debate exists over the traumatic but questionable side effects attributed to the use of levodopa in such patients. More data are needed on the psychic effects of levodopa, but the following points were noted: (1) the proportion of patients exhibiting such effects depends on the criteria used to select patients; (2) the psyches of some patients deteriorate from the fact of being hospitalized and levodopa may be falsely accused as the cause; (3) a depressive reaction, from whatever the cause, may follow the initiation of levodopa therapy; and (4) other drugs and foodstuffs identified have also been reported to affect the actions of levodopa. The reported clinical experience does not show the last point to be the case. 8 references.

092004 Lowenstein, Leah M.; Simone, Rosemary; Boulter, Phillip; Nathan, Peter. 15 Stoughton Street, Boston, Massachusetts 02118 Effect of fructose on alcohol concentrations in the blood of man. *Journal of the American Medical Association.* 213(11):1899-1901, 1970.

Fructose infusions for reducing morbidly high concentrations of alcohol in the blood are evaluated in a study with 12 volunteer males aged 30 to 45 years who were chronic alcoholics. Fructose infusions are suggested for managing patients in emergency wards who need sobering up before treatment of their other complications. Fructose has been found the most effective experimental compound for increasing the metabolism of alcohol (ethanol). The subjects had been sober for more than 3 weeks before infusions of fructose, glucose, or saline solutions were administered intravenously, simultaneous with the subjects drinking 300 milliliters of bourbon. Patients given fructose infusions had their alcohol levels lowered by 43%, compared to subjects given saline solutions. Glucose infusions were ineffective. The lowering of the alcohol levels by fructose may occur because the dissociation of the alcohol dehydrogenase-NADH complex is accelerated by intermediary metabolites of fructose. 12 references. (author abstract modified)

092306 Pernhaupt, G.; Quatember, R. Psychiatrische-Neurologische Universitatsklinik, Lazarettgasse 14, A-1090 Wien 1X, Austria Pharmaco-psychological contribution to the clinical use of a psycho-sedative./ Pharmakopsychologischer Beitrag zur klinischen Anwendung eines Psychosedativums. *Wiener Medizinische Wochenschrift (Wien).* 120(42/43)737-740, 1970.

The effectiveness of psychosedatives on various performance levels was tested in 50 patients suffering from psychiatric and clinical psychological disorders. A comprehensive battery of tests was applied, yielding a general improvement in areas of attention, concentration and psychomotor response. No effect was noted in cases of pronounced depression. 20 references. (Author abstract modified)

092974 Kales, Anthony; Ansel, Robert D.; Markham, Charles H.; Scharf, Martin B.; Tan, Tjiauw-Ling. University of California Los Angeles School of Medicine, Los Angeles, California Sleep in patients with Parkinson's disease and normal subjects prior to and following levodopa administration. *Clinical Pharmacology and Therapeutics.* 12(2):397-406, 1970.

Six patients with parkinsonism and 4 spouse control subjects were studied in the sleep laboratory prior to administration of levodopa and during initial, short-term, long-term, and chronic usage. The parkinsonian patients had a significant amount of sleeping difficulty, taking much longer to fall asleep and awakening frequently for long periods during the night, as compared with spouse control subjects and a normal, elderly control group. Values for rapid eye movement (REM) sleep were similar to those of both control groups, while stage 3 sleep was decreased. Three of the 6 patients showed a decrease in REM sleep with initial drug administration at the 1.0gm. per day dosage level. One had a marked increase in REM sleep for about the first 2 weeks of drug administration. However, REM sleep values for all patients with long-term and chronic drug administration were similar to baseline values. In the spouse control subjects, other than a slight increase in REM sleep with initial drug administration which was not maintained with long-term use, no changes were noted in REM sleep, even during withdrawal of the drug. In both patients and control subjects, values for sleep induction and sleep maintenance were essentially unaltered by the administration of levodopa. Biochemical implications of these data are discussed. In addition, the clinical implications in terms of evaluating and treating the moderately severe insomnia in parkinsonian patients are described. 15 references. (Author abstract)

093540 Bahr, F.; Ilanos R.; Matussek, N. Instituto Max-Planck, Psiquiatria de Munich, Munich, Germany /Quantative clinical analysis of the effect of fenetyllin (Captagon) on hyperkinetic children./ Analisis clinico cuantitativo del efecto de la fenetilina (Captagon) sobre los ninos hiperquineticos. *Revista de Neuro-Psiquiatria (Lima).* 33(3):233-242, 1970.

Ten hyperkinetic children were treated in a double blind study with Fenetylin = Ftl (Captagon R). The effect of the treatment was quantitatively estimated with a time-recorder, a movement recorder and with a rating scale. The daily dosage was 50 - 150 mg. (1-3 tablets) except for 1 child who received a 250 mg. dosage. During the hospitalization 6 children showed a substantial to very good improvement, 3 children were improved only in some aspects and in 1 child a deterioration was found. In addition to a decrease in motor activity, aggressive behavior also decreased. Furthermore, more patience, endurance and emotional stability were observed. A too large dosage of Ft led to loss of appetite and weeping. In 3 cases in which, after a successful treatment the children were sent home, the therapeutic effects remained stable. 17 references. (Journal abstract)

093689 Carlson, Lars A.; Levi, Lennart; Ryd, Eva; Tord, Inga. author address not given Effect of nicotinic acid combined with a tranquillizer (hydroxyzine) on serum lipid levels and urinary catecholamine excretion in geriatric patients. *Reports from the Laboratory for Clinical Stress Research (Stockholm).* No.19:1-11, 1970.

The purpose of this study was to follow plasma lipids, urinary catecholamine excretion, and the clinical response to treatment with hydroxyzine and nicotinic acid in geriatric patients; and to investigate whether hydroxyzine augments the lipid lowering effect of nicotinic acid. None of the treatments used had any effect on urinary excretion of adrenaline or noradrenaline, on body weight, or on ratings of restlessness, confusion, or bodily complaints. Hydroxyzine did not affect plasma lipid levels or augment nicotinic acid effect. 23 references. (author abstract modified)

093919 Janz, D. Universitats-Nervenklinik, Vossstrasse 2, 69 Heidelberg, Germany /Antiepileptic dosing after excessive alcohol intake./ Antiepileptikadosierung nach Alkoholexzess. *Deutsche Medizinische Wochenschrift (Stuttgart).* No.12:651, 1970.

An answer is given to the question of whether an epileptic taking a high dosage of anticonvulsant medication 3 times daily, such as valium, epanutin, luminal, or distraneurin, who as a result of imbibing alcohol to excess experiences an epileptic seizure still can be given the same drug dosage parenterally. The contention is that since experience has shown that epileptic attacks occur not during alcoholic stupor but rather after emerging from an inebriated state, it is possible to treat the seizure in the customary manner. If breathing and circulation are not seriously affected, the usual dosage can be administered. The dosage can and should be altered according to indications. However, 300mg of zentropil or 750mg of mylepsinum are not considered excessively high.

094305 Reda, G. C.; Cancrini, L.; Bertoletti, P.; Dotti, A.; Scapicchio, P. L.; Tesei, R. Instituto di

Psichiatria, Universita di Roma, Rome, Italy /Clinical and pharmacological contribution to the study of alcohol-imipramine and alcohol-thioproperazine associations./ Contributo clinico e sperimentale allo studio delle associazioni alcool-tioproperazina ed alcool-imipramina. *Alcoholism (Zagreb).* 6(1):45-53, 1970.

The effects of alcohol - imipramine and alcohol -thioproperazine associations in rats were studied. Observations showed that 1) the verification of different or even contrary types of interaction, when the study was carried out with different tests and in analogous experimental situations, in the case of alcohol -imipramine association, and 2) the verification of a characteristic summation of effects in alcohol -thioproperazineassociation. Preliminary data concerning the study of the same associations in humans are presented. The difficulty of an immediate correlation of these data with precedents is briefly discussed from the methodological and interpretative viewpoint. 7 references. (Journal abstract)

094423 Taverna, P.; Ferrari, G. Clinica Psichiatrica, Universita di Pavia, Voghera, 27058 Italy /Clinical experiment with a new tranquillizer: trioxazine./ Sperimentazione clinica di un nuovo tranquillante: la trioxazina. *Minerva Medica (Torino).* 61(46):2574-2590, 1970.

The favorable results obtained in 50 patients with clinical symptoms of anxiety or erethism (neurotic, psychoneurotic, depressed and alcoholic subjects) submitted to a controlled clinical experiment with Trioxazine and compared with a placebo and meprobamate are reported. These data agree with those deduced from the literature. 37 references. (Journal abstract)

094978 Klett, C. James; Hollister, Leo E.; Caffey, Eugene M., Jr.; Kaim, Samuel C. Central Neuropsychiatric Research Laboratory, Perry Point, Maryland Evaluating changes in symptoms during acute alcohol withdrawal. Perry Point, Md., Cent. Neuropsychiatric Res. Lab., 1970. 14 p.

A study of changes in symptoms during acute alcohol withdrawal is discussed. Male patients experiencing the symptoms of acute alcohol withdrawal were assigned at random to double-blind treatment with chlordiazepozide, chlorpromazine, hydroxyzine, thiamine or placebo for a period of 10 days. They were rated 3 times daily by nursing personnel using a Nurses' Rating Scale and were asked to complete a Mood Scale daily. Patients generally showed a rapid improvement in different symptom areas regardless of the group to which they had been assigned. Treatment comparisons suggested that fewer symptoms were associated with placebo and thiamine treatment than with the 3 psychoactive drugs. However, the greater incidence of convulsions and delirium occurring in these 2 groups as compared with the chlordiazepoxide group more than offsets any advantage that may exist for what is essentially supportive treatment. 2 references. (Author abstract modified)

097974 Brohult, Johan; Levi, Lennart; Reichard, Hans. Lab. for Clinical Stress Research, Karolinska Sjukhuset, Stockholm, Sweden Urinary excretion of adrenal hormones in man: effects of ethanol ingestion, and their modification by chlormethiazole. *Acta Medica Scandinavica (Kobenhavn).* 188:5-13, 1970.

A large single dose of ethanol (approximately 500 ml brand whisky) was administered to 9 young, healthy males. This stimulus provoked pronounced increases in adrenaline and noradrenaline excretion during and soon after the ethanol ingestion. Similarly, the hangover next morning was accompanied by marked increases in adrenaline and noradrenaline excretion levels, in addition to increased excretion rates of 17 hydroycorticosteroids. In 5 subjects treated with 0.5g chlormethiazole, the catecholamine increases during the hangover period were significantly reduced. During the week following the ethanol ingestion, the increase in adrenal function tended to persist. Some theoretical and clinical implications of these findings are discussed and some indications in favor of a relationship between the emotional behavioral and the physiological effects of ethanol ingestion are mentioned. (Journal abstract - USGRDR)

097985 Oliveros, R. T.; Ban, T. A.; Lehmann, H. E.; Sterlin, C.; Saxena, B. M. Hopital des Laurentides, l'Annonciation, Quebec, Canada Thiothixene: its range of therapeutic activity. *Int. Z. fur klinische Pharmakologie, Therapie und Toxikologie (Munchen).* 3(1):26-29, 1970.

The efficacy of thiothixene in the treatment of psychiatric patients was examined in a 12 week clinical study on 49 male and 11 female patients. Twenty had schizophrenia, 10 psychotic depression, 10 psychotic neurosis and 20 were geriatric patients. Thirty had acute disease, the rest were

chronic. Thiothixene was given orally in doses of 2-4mg/day. All patients were hospitalized. The therapeutic effects of thiothixene were most impressive in the schizophrenics. In psycho- neurotic reactions, the therapeutic effectiveness, at least in certain areas, wore off after a few weeks. In psychic depression, only the psychotic traits associated with the dysthymic manifestations were affected. The therapeutic efficacy seemed to be independent of the extrapyramidal symptom reducing action, but the occurrence of extrapyramidal symptoms under the influence of the drug was apparently related to organic changes in the brain. 24 references. (Author abstract modified)

099957 Carlsson, Carl; Johanson, T. Clinic II, Lillhagen Hospital, 422 03 Hisings Backa, Sweden Effects of propranolol (Inderal) on psychiatric symptoms in chronic alcoholism. ***Acta Psychiatrica Scandinavica (Supplement)(Kobenhavn).*** **No.217:58, 1970.**

Symptoms such as anxiety, depression and dysphoria are often found among alcoholics and especially in the withdrawal phase symptoms of high sympaticus-activity are common, particularly tachycardia, hyperkinetic circulation, perspiration. In other states of anxiety propranolol (Inderal) has proved to be effective not only on circulation but also on psychiatric symptoms. Disturbances in the catecholamine metabolism are known in alcoholism and other kinds of addiction. In open clinical tests a marked effect of decreasing anxiety was observed when 36 chronic alcoholics were examined 3 times by a psychologist with questionnaires and observation. The patients received double-blind 40mg X 4 propranolol and placebo. Clear distinctions were observed in the questionnaires after 3 weeks. For the placebo group the improvement points for the symptom of anxiety were 22, for depression 11. Corresponding figures for the propranolol group were 61, 70 respectively. Obtained with symptoms of dysphoria were 33 from the placebo group and 27 from the propranolol group. It seems that propranolol should be of therapeutic value in the treatment of alcoholics. No serious side effects have been observed. (Author abstract modified)

100020 Malm, Ulf. Lillhagen Hospital, 422 03 Hisings Backa, Sweden Possible applications of long-acting intramuscular major tranquillizers. ***Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).*** **No.217:54-55, 1970.**

There are now phenothiazine derivatives, butyrophenones and thiaxanthene derivatives prepared for intramuscular administration with effectiveness lasting from 1-4 weeks. In maintenance treatment outside the hospital, and in studies of the values of prophylactic and/or curative pharmacotherapy, the factor to be measured can be kept under control with reasonable assurance. In schizophrenia research aimed at comparing different methods of treatment, how the patient fares in communal surroundings is important. Where the patient is about to be discharged from the hospital, or is an outpatient, treatment by long acting major tranquillizers can be the therapy indicated. Violently acute manic and schizophrenic psychotic patients with highly disturbed behavior patterns form an important group, often prejudiced, against all intake of drugs. Here, large does of fluphenazine enanthate offer good prospects of immediate therapeutic gains. Ambulatory patients suffering from geriopsychiatric illnesses with paranoic reactions and memory disturbances, and patients addicted to the tablet habit who are in need of psychopharmacotherapy, but who create problems of overdosing, long acting intramuscular major tranquilizers can be helpful. Intermittent intramuscular administration of major tranquilizers can be used to maintain regular contact with those groups of patients in need of regular care. There is a risk that acute side effects may occur several days after a patient has been given a major tranquilizer. Complications may also arise in accident cases, or in cases with acute physical illnesses. (Author abstract modified)

12 PSYCHOTOMIMETIC EVALUATION STUDIES

097286 Pahnke, Walter N.; Kurland, Albert A.; Unger, Sanford; Savage, Charles; Grof, Stanislav. Maryland Psychiatric Research Center, Box 3235, Baltimore, Maryland 21228 The experimental use of psychedelic (LSD) psychotherapy. ***Journal of the American Medical Association.*** **212(11):1856-1863, 1970.**

In a report on experiments, research projects, and literature on the use of psychedelic drugs in psychotherapy, several areas of study are discussed: (1) effects in man facilitated by psychedelic drugs; (2) varieties of therapies with psychedelic drugs; (3) the question of safety and genetics; and (4) medical and social comment. Psychedelic - peak psychotherapy research projects are described, including presentation of an

extensive case history. Available evidence on the efficacy of psychedelic drugs as therapeutic tools for treating mental illness is conflicting, due in part to the differing research methods that are not replicated among the many teams working in the field. Onepoint, however, has been clearly shown: LSD is not a substitute for skilled psychotherapy, although LSD can enhance a therapy program of sufficient duration. Further research on the use of psychedelic drugs is called for. 32 references.

13 MECHANISM OF ACTION: PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

089438 Gerson, Irvin M.; Friedman, Ronald; Unterberger, Herbert. Philadelphia State Hospital, Philadelphia, Pennsylvania Non-antagonism of antiadrenergic agents by a dibenzoxepine: preliminary report. *Diseases of the Nervous System.* 31(11):780-782, 1970.

A study designed to explore possible drug interaction between a dibenzoxepine and antiadrenergic, antihypertensive drugs is made. The patients were male and female hypertensives stabilized on guanethidine or methyldopa. Doxepin was shown to produce no significant interference with representative antiadrenergic, antihypertensive therapeutic agents such as guanethidine and methyldopa. 10 references. (Author abstract modified)

089788 Saji, Y.; Chiba, S.; Takeo, Y.; Yui, T. Research and Development Division, Takeda Chemical Industries Ltd., Juso-Nishinocho, Higashiyodogako-ku, Osaka, Japan Possible loci of action of 2-ethyl-ethylamino-6-methoxy-s-triazine for electroencephalographic and sympathetic activation in cat. *Arzneimittel-Forschung (Aulendorf/Wurtt).* 20(10):1591-1594, 1970.

A possible site of action of 2-ethyl-4-ethylamino-6-methoxy-s-triazine (EEM) in effecting electroencephalographic (EEG) sympathetic activation in cat was delineated. Previous studies of EEM revealed that it produced definite and persistent EEG activation which was accompanied by depressive behavior. Furthermore, the disrupting activity of this compound on conditioned avoidance behavior in rats was counteracted by atropine, suggesting that a cholinergic mechanism was involved at least partly in the central action of EEM. In this study, transection of the brain disclosed that the potent site of action of EEM was the brainstem. Complete blockage of the EEG activation by atropine, a cholinolytic agent, implicated the presence of a cholinergic mechanism in the ascending pathway from the brainstem. The sympathetic excitatory action of this compound, as indicated by the recurrent contractions of the nicitating membrane and elevation of the blood pressure level, was proved to be set up via the posterior hypothalamus in experiments which recorded directly the electrical discharge of the progan-glionic cervical sympathetic nerve of the cat preparations with truncated brain of limited lesion. 22 references. (Author abstract modified)

090052 No author. Author address not given Norepinephrine turnover in brain after administration of imipramine: enhancement by thyroid hormone. *Connecticut Medicine.* 34(7):465-466, 1970.

A relative deficiency of norepinephrine or other biogenic amines at critical receptors in the brain may occur in some depressive disorders. Antidepressants, such as imipramine, may cause changes in biogenic amine metabolism which may account for their clinical effects. A single dose of imipramine inhibits the uptake of norepinephrine but does not alter the content of endogenous epinephrine. It is suggested imipramine may decrease norepinephrine biosynthesis. It has been found that imipramine administered with small doses of thyroid hormone produces more rapid clinical improvement in depressed patients than does imipramine alone. Thyroid hormone may accelerate the development of changes in turnover and content of norepinephrine in the brain. Long-term administration of imipramine in depressed patients facilitates restoration of normal functioning in spite of relatively reduced concentrations of endogenous norepinephrine by increasing its availability at receptor sites. Thyroxine, other hormones and pharmacological agents or physiological and behavioral techniques which increase the turnover of norepinephrine when administered with tricyclic antidepressant drugs may accelerate the clinical antidepressant effects of these drugs. 2 references.

090068 Kier, Lemont B.; Truitt, Edward B., Jr. Battelle Memorial Institute, 505 King Avenue, Columbus, Ohio 43201 The preferred conformation of dopamine from molecular orbital theory. *Journal of Pharmacology and Experimental Therapeutics.* 174(1):94-98, 1970.

The therapeutic efficacy of dopa in Parkinson's disease is related to its formation of dopamine and not to further change to norepinephrine; the 2 catecholamines are metabolized differently by neural tissues. To determine if there are separate receptors for the 2 molecules, molecular orbitals for each molecule were calculated, and an analysis of the conformation of dopamine hydrochloride in solution was made with high resolution nuclear magnetic resonance in deuterium oxide at 39 degrees Centigrade. In aqueous solution dopamine hydrochloride was found to prefer a gauche and not a trans conformation. The molecular orbital calculations also show an energetic preference for a gauche placement of the nitrogen and phenyl ring. In the norepinephrine molecule, the energetic preference is for a transplacement of the nitrogen and phenyl ring. The finding of 2 distinctly different relationships between the ring and onium group in dopamine and norepinephrine suggests that a different relationship of essential molecular features in each is responsible for biologic action, namely, different receptors for the 2 molecules. 20 references.

090371 Watanabe, A. M.; Chase, T. N.; Cardon, P. V. Laboratory of Clinical Sciences, National Institute of Mental Health, Bethesda, Maryland Effect of L-dopa alone and in combination with an extracerebral decarboxylase inhibitor on blood pressure and some cardiovascular reflexes. ***Clinical Pharmacology and Therapeutics.*** **11(5):740-746, 1970.**

The effect of extracerebral decarboxylase inhibition on the hyperternsive reaction of L-dopa and the effect of L-dopa on adrenergically mediated cardiovascular reflexes were studied on 12 patients receiving L-dopa medication for neurologic or psychiatric disorders. It was found that L-Dopa produced a significant reduction in recumbent and standing blood pressure in patients with neurologic or psychiatric disorders. The addition of an extracerebral decarboxylase inhibitor potentiated this effect. Reflex forearm arteriolar and venous constriction was present during therapy with L-dopa alone or in combination with the decarboxylase inhibitor, but there was an attenuation of reflex forearm arteriolar constriction. It is suggested that the hypotensive effect of L-dopa may be mediated through the central nervous system. 17 references. (author abstract modified)

090427 Ebert, William R.; Morris, Robert W.; Rowles, Susan G.; Russell, Henry T.; Born, Gordon S.; Christian, John E. Research and Development Department, Philips Roxane Laboratories, Columbus, Ohio 43216 In vivo evaluation of absorption and excretion of pentylenetetrazol -10-14C from sustained-release and nonsustained-release tablets. ***Journal of Pharmaceutical Sciences.*** **59(10):1409-1412, 1970.**

Sustained release and nonsustained release tablets containing pentylenetetrazol-10-14C were administered orally to human volunteers. The levels of the drug and/or its labeled metabolites in the plasma and urine were determined by liquid scintillation counting. These data showed that the sustained release tablets provided a consistent plasma level of 14C for about 12 hr and that the drug and/or its labeled metabolites were excreted in the urine at a fairly constant rate during this period. The nonsustained release tablets given in divided doses resulted in 3 separate peak plasma-14C levels and a urinary excretion pattern similar to that of the sustained release tablet. A single dose of the nonsustained release tablet was followed by a peak plasma-14C level, which decreased during the 12 hr after administration, and by a fairly constant rate of urinary excretion of 14C during this period. 8 references. (author abstract)

092889 Kopin, Irwin J. Laboratory of Clinical Science, National Institute of Mental Health, Building 10, Bethesda, Maryland 20014 Effect of drugs on catecholamine synthesis (Unpublished paper). Bethesda, Maryland, NIMH, 1970. 11 p.

The effects of drugs on catecholamine synthesis are reviewed and discussed. To aid in the understanding of the effects of drugs on catecholamine turnover, current concepts of the function of the adrenergic neurone and the processes involved in the synthesis, storage, release, inactivation and metabolism of the neurotransmitter are reviewed. Enzyme activity involved in the synthesis of norepinephrine and direct or indirect effects of drugs on these enzymes are discussed. Based on the concepts of the adrenergic neurone, it is believed that the effects of drugs on norepinephrine synthesis rates may be related to their mechanisms of action at a molecular level. The enzymes or biochemical process involved in catecholamine biosynthesis which are inhibited, the inhibiting drug, and the mechanism of inhibition are presented tabularly,

as are the indirect effects of drugs on catecholamine biosynthesis. The mechanisms and agents are summarized for the latter. Effects of drugs on dopamine metabolism are included in the review and discussion. It is concluded that the relationship of psychoactive drugs to alterations in the synthesis and utilization of catecholamines has provided an attractive array of evidence supporting the hypothesis that these amines play an important role in brain function and have been the basis of hopes that such agents may be useful in treatment of a wide variety of psychiatric and neurological disorders. It is hoped that further elucidation of the role of amines in psychiatric disorders may lead to appropriate therapeutic agents to correct metabolic bases of mental illness. 21 references.

093000 Martin, William R. National Institute of Mental Health Addiction Research Center, Lexington, Kentucky Pathophysiology of narcotic addiction; possible roles of protracted abstinence in relapse (Unpublished paper). Lexington, Kentucky, NIMH, 1970. 13 p.

Experiments that bear on the hypothesis that chronic use of narcotic analgesics may induce long lasting physiologic changes are summarized. Also presented is evidence that these long lasting physiologic changes are associated with an increased responsivity to stress, and it is suggested that this increased responsivity to stress is responsible in part, either directly or indirectly, for relapse to narcotics and other forms of deviant behavior. A study designed to characterize the early and protracted morphine abstinence syndrome in the rat is reviewed and biochemical and physiologic effects are described. Studies to test the hypothesis that abstinence signs could be conditioned in rats suggested that chronic administration of morphine and subsequent withdrawal are associated with long persisting physiologic changes, alterations in the metabolism of epinephrine and norepinephrine by the adrenal glands and perhaps the brain, and a need for narcotics by the rat. The early and protracted abstinence syndromes in man were investigated and the physiologic and biochemic effects are summarized. The clinical significance of the findings reviewed is not clearly understood. The protracted abstinence syndrome has been shown to persist for many months (over 4) after withdrawal of morphine in both man and rat. The findings do not prove that the Ss are hyperresponsive to stress during protracted abstinence, yet they are consistent with the hypothesis. Characteristics of new methodologies which are believed to be necessary to critically test the relevance of the theories concerning the role of protracted abstinence and conditioning to relapse are suggested. 13 references.

094472 Ferrari, G. Clinica delle Malattie Nervose e Mentali, Universita di Bologna, Bologna, Italy /The use of the pyrimidine nucleosides (cytidine and uridine) in the therapy of cerebral vascular illness./ L'impiego dei nucleosidi pirimidinici (citidina e uridina) nella terapia delle malattie vascolari cerebrali. *Rivista Sperimentale di Freniatria (Milano).* 94(1):207-216, 1970.

The results obtained using a preparation composed of pyrimidine nucleosides (cytidine and uridine) in a group of patients affected with vascular encephalopathies including 4 cases of cerebral arteriosclerosis, 5 cases of demential syndrome, and 13 cases of hemipares or pyrimidal hemiplegia are presented. Such a therapeutic method is based on some experimental data which have documented the important metabolic action of the pyrimidine nucleosides as being forerunners of ribonucleic acid and nucleotides and their intervention in the metabolism of carbohydrates at the level of the nervous tissue and is also justified by the already known fact of the diminuation of the cerebral consummation of glucose in the course of vascular encephalopathies. In 75% of the cases the clinic report has been favorably influenced by the administration in the drug. 28 references. (Journal abstract)

094962 Kanig, Karl. Abteilung fur Neurochemie der Universitatsnervenklinik, 665 Homburg/Saar, Germany /On the biochemical mechanism of action of nicotinic acid, nicotineamide, methionine, and d-penicillamine in the treatment of psychoses./ Zum biochemischen Wirkungsmechanismus von Nictinsaure, Nicotinamid, Methionin und D-Penicillamin bei der Behandlung von Psychosen. *Arzneimittel-Forschung (Aulendorf/Wurtt).* 20:909-911, 1970.

The nature of the biochemical role played by nicotinic acid, nicotineamide, methionine, and D-penicillamine in the treatment of psychoses is discussed. These substances are observed to influence psychotic symptoms in a closely similar manner. An attempt is made to demonstrate a common biological mechanism by which all 4 substances may act. Possibly, it consists of an in-

fluence on tryptophane metabolism in favor of tryptamine and its derivatives or of derivatives of 5-hydroxytryptamine. 6 references. (Author abstract modified)

097963 van Praag, H. M.; Korf, J.; van Woudenberg, F. Department of Biological Psychiatry, Psychiatric University Clinic, Oostesingel 59, Groningen, The Netherlands Investigation into the possible influence of chlorinated amphetamine derivatives on 5-hydroxytryptamine synthesis in man. ***Psychopharmacologia (Berlin).*** **18(4):412-420, 1970.**

An investigation into the possible influence of chlorinated amphetamine derivatives on 5-hydroxytryptamine (5-HT) synthesis in man is made. It has been shown in test animals that 4-chloro-N-methylamphetamine (CMA) and 4-chloroamphetamine (4-CA) cause a decrease in the cerebral 5-HT and 5-hydroxyindolaecetic acid concentrations. In man, these compounds have a therapeutic effect on depression. In terms of antidepressant effect, they resemble not so much the nonchlorinated amphetamine derivatives as the true antidepressants. This consideration of the question whether the influences of CMA and 4-CA on the 5-HT metabolism is based on inhibition of 5-HT synthesis. No arguments to support this hypothesis were found; findings obtained did not support the postulate that these compounds are 5-HT depletors. In conclusion, a possible explanation of the antidepressant effect of chlorinated amphetamine derivatives is offered. 33 references. (Author abstract modified)

098039 Ambrozi, L.; Birkmayer, W. Neurologische Abt. des Alterskrankenhauses der Stadt Wien-Lainz, Versorgungsheimplatz 1, Vienna XIII, Austria /The objective evaluation of psychpharmacological drugs with caffeine and caffeine-free coffee as an example./ Uber die Objektivierbarkeit von psychopharmakologischen drogen am Beispiel von Coffein und coffeinfreiem Kaffee. ***Int. Z. fur klinische Pharmakologie, Therapie und Toxikologie (Munchen).*** **3(2):167-173, 1970.**

The testing of caffeine - containing coffee and caffeine -free coffee is 45 healthy Ss, free from any circulatory disturbance, is presented. The testing of motor strength by the physiological acceleration transducer; the afferent perception ability with the flicker fusion frequency apparatus; the affective emotional reactivity with the psychogalvanic skin reflex apparatus; and changes in respect0i- ration, pulse and blood pressure with a polygraph apparatus, was effected before and after either beverage. Following caffeine - containing coffee, there is a significant increase in the kinetic energy which can be mobilized, and a significant reduction in affective reactivity. Respiration, pulse and blood pressure do not show anysignificant variation due to caffeine. The substitution of caffeine - free coffee in patients reacting to caffeine is recommended, since the caffeine - free beverage has no effect on any of the areas tested. 24 references. (Author abstract modified)

100026 Gram, Lars F.; Kofod, B.; Christiansen, J.; Rafaelsen, O.J. Psychochemistry Institute, Rigshospitalet, 2100 Copenhagen O, Denmark Factors affecting the urinary excretion of tricyclic antidepressants in man. ***Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).*** **No.217:51, 1970.**

The urinary excretion of 14C-labelled antidepressive drugs has been investigated in man by a method for combined quantitative and qualitative determination of metabolites. On an average 40% of an administered test dose of 14C-imipramine were found in the first 24 hour specimen, and about 70% was excreted by the end of 3 days. The metabolites were separated into 3 fractions; nonconjugated, conjugated, and nonextractable metabolites. By thin layer chromatography about 10 nonconjugated and 10 conjugated metabolites were isolated. The excretion patterns showed considerable individual variations. The excretion pattern was sensitive to changes in urinary pH -- acidification of the urine increased the total excretion 10-50%. This increase was due to a 50-100% increase in excretion of nonconjugated metabolites. Among the nonconjugated metabolites, the excretion of unchanged imipramine and desmethylimipramine was sensitive to changes in urinary pH. The excretion rate was faster after oral administration of the test dose than after intravenous administration. This indicates that urinary excretion depends on liver metabolism of the drug. When the subjects were concurrently treated with neuroleptic drugs (perphenazine and haloperidol), the excretion rate was markedly reduced (30-40%) and the difference between orally and intravenously administered drug almost disappeared. A positive relationship between the excretion rates of imipramine, amitriptyline, and chlorimipramine

and the clinically used dosages of these drugs has been found. (Journal abstract)

14 MECHANISM OF ACTION: BEHAVIORAL

089784 Gerstenbrand, F.; Grunberger, J. Psychiatrisch-neurologische Universitatsklinik, Spitalgasse 23, A-1090 Wien 1X, Austria /Clinical experience with Mesoridazin in the therapy and rehabilitation of traumatic frontal brain damage./ Klinische Erfahrungen mit Mesoridazin in der Therapie und Rehabilitation von traumatischen Frontalhirnschaden. *Wiener Medizinische Wochenschrift (Wien).* 120(42/43):732-737, 1970.

Findings in the clinical use of the medium tranquillizer Mesoridazine (Lidanil) in the therapy and rehabilitation of traumatic frontal brain damage are discussed. The drug exerted a beneficial effect on the 62 patients tested, and in 20 of these, subjected to a variety of psychological tests, the clinical effects of the drug were controlled and the findings confirmed. The nature of its effects and the possible influence of the recticular formations of the brain are discussed. 14 references. (Author abstract modified)

089859 Vetter G. Klinik Auerbach, 6142 Bensheim-Auerbach/Bergstr., Heinrichstr. 4, Germany /Psychosomatic factors in rheumatic disorders and their relief by medication./ Psychsomatische Storfaktoren bei rheumatischen Erkrankungen und ihre medikamentose Beeinflussung. *Medizinische Welt (Stuttgart).* 21(40):1749-1750, 1970.

The effects of diazepam on the psychosomatic symptoms which accompany rheumatic disorders were studied. Ss were 150 patients. A psychometric test, the Minnesota Multiphasic Personality Inventory, administered after therapy, showed a positive influence on 4 scales: hypochondria, depression, hysteria, and psychasthenia. 16 references. (Journal abstract modified)

091138 Gentili, E. Clinica delle Malattie Nervose e Mentali dell'Universita di Milano, Milan, Italy /Pharmacological association of thioridazine-hydergine in pschoemotional troubles of the aged./ Su un prodotto di associazione farmacologica (Tioridazina-hydergina) nelle turbe psicoemotive dei senili. *Rassegna de Studi Psichiatrica (Siena).* 59(5-6):497-506, 1970.

The results obtained with the association thioridazine-hydergine (Visergil) on 40 ambulatory aged patients, presenting character and emotional disturbances, are reported. The therapeutic effectiveness, the lack of side effects, the nontoxicity make the drug very important in psychoemotional and character troubles of the aged. 18 references. (Journal abstract)

092481 Villani, M.; Botteghelli, R. Via Castaldi, 3-34137, Trieste, Italy /Electrocardiographic data in chronic alcoholism before, during and after treatment with tetraethylthiuramdisulphide./ Studio dell'elettrocardiogramma nell'etilismo cronico (prima, durante e dopo trattamento con tetraetiltiuramidisolfuro). *Minerva Medica (Torino).* 61(95):5425-5431, 1970.

The effect of alcoholism on the development of arteriosclerosis and on the myocardium is a matter for discussion at the present time. Symptoms and clinical signs observed in a number of chronic alcoholics have been grouped into a profile called 'alcoholic cardiomyopathy' by Evans. Other workers have distinguished alcoholic myocardosis from cardiac signs attributable to the nutritional deficiency states so commonly observed in chronic alcoholism. Systematic findings in 100 chronic alcoholics of both sexes aged from 25 to 67 yr undergoing tetraethylthiuramdisulphide voluntary withdrawal syndrome normally described as a variant within the limits of normal due to vagal hypertonia. This is, however, so characteristic, if not pathognomonic, as to suggest that the attitude towards alcohol of all persons presenting such a picture should be investigated. 20 references. (Journal abstract)

093537 Dufrasne, M.; Fraipont, J.; Ferriere, G. author address not given. /The use of narco-analysis in diagnostic psychiatric technique./ Interet de la narco-analyse et des techniques apparentees en propedeutique psychiatrique. *Feuillets Psychiatriques de Liege (Liege).* 3(4):516-529, 1970.

Techniques of narcoanalysis are discussed in terms of their diagnostic interest. Four case synopses are presented in which a diagnosis could not be adequately determined by other means within the time limits required by the medicolegal situation. Type of pathology, agents used to induce subnarcosis, regimen of administration, and results are discussed for each.

094467 Cavalca, G. G.; Bonasegla, F.; Guaraldi, G. P. Clinica delle Malattie Nervose e Mentali, Universita di Modena, Modena, Italy /Concerning

a case of thrombosis of the middle cerebral artery in the course of progestinic treatment./ Su di un caso di trombosi dell'arteria cerebrale media in corso di trattamento progestinico. ***Rivista Sperimentale di Freniatria (Milano).*** **94(1):83-94, 1970.**

A case of thrombosis of the middle cerebral artery, in a young woman during the treatment with progestinics for anticonceptional purposes is described. On the basis of the data drawn by the existing literature, the possibility of a pathogenetic relation between the administration of progestinics and the arising of thrombotic diseases of the brain arteries is discussed. 30 references. (Journal abstract)

094610 Academia Peruana de Medicina; Trelles, J. O.; M. Trelles, Luis; Querol, Mariano; Ramirez del Villar, Eduardo; Saavedra, Alfredo; Mori, Grover. Lima, Peru /Somapsychic relations in medicine: session of homage of the Peruvian Academy of Medicine to Professor Honorio Delgado./ Relaciones somato-psiquicas en medicina: sesion de homenaje de la Academia Peruana de Medicina al Profesor Honorio Delgado. ***Revista de Neuro-Psiquiatria (Lima).*** **33(1):1-30, 1970.**

A meeting of the Peruvian Academy of Medicine held to pay homage to the late academatician, Professor Honorio Delgado, is reported. Psychosomatic medicine was reviewed from the following veiwpoints: neurological, electroencephalographical, pharmacological, psychiatrical, and neo-Hippocratic. 58 references. (Journal abstract)

095655 Liesiene, V. A. Otdel Neyrofiziologii, Kaunasskogo Meditsinskogo Instituta, Kaunas, U. S. S. R. /Comparative study of natural sleep and the action of phenamine and chlorpromazine evaluation of the mean extreme's frequency of ECoG in cats./ Sravneniye faz yestestvennogo sna s deystviyem fenamina i aminazina i otsenka sredney chastoty ekstremumov EKoG koshki. ***Farmakologiya i Tosikologiya (Moskva).*** **33(6):665-669, 1970.**

A comparative study of the mean extrema's frequency (MEF) and mean ECG amplitude (MA) was carried out on unrestrained cats with implanted electrodes during natural sleep and under the effect of phenamine (5mg/kg) and chlorpromazine (15mg/kg). The ECG and its MA during slow wave sleep (SWS) were similar to those registered under the effect of chlorpromazine. The MEF levels during low voltage fast wave or paradoxical sleep (PS) and that of the phenamine effect were similar to and higher than the MEF level with the cats staying awake. There were no differences between visual ECG evaluation or its MA in the 2 aforementioned cases. The results show similarity between the cortical activity during PS and under the effect ofphenamine, on one hand, and the differences during SWS and under the action of chlorpromazine, on the other. 20 references. (Journal abstract)

095719 Dede, Giulio. Istituto di Medicina Legale e delle Assicurazioni, Universita di Messina, Messina, Italy /Casuistic contributions on the use of a drug in criminology on dissociality and on minor irregular behavior./ Contributo casistico all'impiego in criminologia di uno psicofarmaco della socievolezza su minori irregolari della condotta. ***Quaderni di Criminologia (Roma).*** **12(1):83-95, 1970.**

A total of 12 children, showing serious irregular behavior and dissociality were treated with Floretione (Caducid Wassermann), for 3 to 6 months and in daily doses of 300 to 600mg. Floretione proved to be really efficient in all treated cases and, particularly, a very rapid action in adjusting the irregular behavior with the environment in those cases where some alterations due to organic causes existed before. The socializing action of the medicine proved to be efficient also in psychological tests because of a lysis action of the main troubles caused by an altered emotionality. This product was borne well and no collateral effect was remarked. From a medical, juridical, criminological and sociological point of view, an actual possibility of using profitably this medicine is envisaged, thanks to its capacity of preventing potential criminals. In effect, it proved to be particularly efficient in fighting those morbid symptoms on which criminality and dissociality in the syndromes of irregular behavior during the evolutive age, are based. 37 references. (Journal abstract)

097655 LeVann, L. J. University of Alberta, Edmonton, Alberta, Canada Clinical experience with Tarasan and thioridazine in mentally retarded children -- a comparative double blind study. ***Applied Therapeutics.*** **12(5):30-33, 1970.**

A double-blind crossover study was conducted among 60 hospitalized mentally retarded children, comparing the drug Tarasan (chlorprothixene) with thioridazine suspensions. Tarasan appeared to: (1) have a broader spectrum of activity as an

antidepressant and tranquilizer; (2) be successful in treating emotional disturbances in the retarded children; (3) induce a rapid response; and (4) lead to little incidence of side effects. Tarasan showed the greatest reduction in the behavioral symptoms of aggressiveness, hostility, and overacidity, which were largely controlled by the third week of therapy. In contrast, improvements among patients given the thioridazine suspensions began to level off and in some cases retrograde in the sixth week, although not significantly. Had the study continued, it is felt that the results would have been substantiated more. Study methods are discussed and findings are extensively tabulated and graphed. 8 references.

097961 Haertzen, Charles A. National Institute of Mental Health, Addiction Research Center, P. O. Box 2000, Lexington, Kentucky 40507 Subjective effects of narcotic antagonists cyclazocine and nalorphine on the Addiction Research Center Inventory (ARCI). ***Psychopharmacologia (Berlin).*** **18(4):366-377, 1970.**

The subjective effects of 2 doses of the narcotic antagonists, cyclazocine (0.6mg and 1.2mg/kg) and nalorphine (16 and 32mg/kg), and of no drug and of placebo were compared with 32 opiate addicts using drug sensitive scales of the addiction research center inventory (ARCI) items. The effects of these narcotic antagonists were highly similar on ARCI scales and items. Both drugs produced a general drug effect, difficulty in focusing eyes, physical weakness, tiredness, poor motivation, moodiness, misery, anxiety, tension, hallucinations, changes in sensation and perception, and inefficiency of physical, cognitive and social functions. Cyclazocine was 15 to 26 times more potent than nalorphine. The effects of cyclazocine and nalorphine were differentiated from the effects of other drugs such as morphine, pentobarbital and lysergic acid diethylamide when the overall pattern of effect was considered. 29 references. (Author abstract modified)

100014 Rafaelsen, Ole J.; Bech, P.; Christiansen, J.; Christrup, Henriette; Nyboe, J.; Rafaelsen, Lise. Psychochemistry Institute, Rigshospitalet, 2100 Copenhagen O, Denmark Cannabis: a psychological and metabolic investigation. ***Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).*** **No.217:61-62, 1970.**

A combination of psychological studies and metabolic investigation of cannabis is prevented. Placebo, cannabis, and alcohol were compared in 10 volunteers, young men 21-27 years old. Psychological testing included short-term memory, mood, time perception, reaction time, and motor coordination. Some of the functions were measured will a car simulator. The test results are compared to qualitative and quantitative urinary excretion of cannabis metabolites determined by thin layer chromatography.(Journal abstract modified)

15 TOXICOLOGY AND SIDE EFFECTS

089443 Denber, Herman C. B. Research Division, Manhattan State Hospital, Ward's Island, New York, N.Y. 10035 An unusual case of chlorpromazine agranulocytosis. ***Clinical and Basic Research.*** **31(11):134-139, 1970.**

An unusual case of agranulocytosis which developed after a long period of treatment with chlorpromazine and various other phenothiazines is described. The patient, a 46 year old female psychotic, had been treated with phenothiazines for over 14 years. A past leucopenic episode was, unfortunately, not known at admission for diagnosis and treatment reported here. It is suggested that agranulocytosis may be a gene linked disorder occurring in about 1:3,000 cases. 19 references. (Author abstract modified)

089785 Bergener, Manfred; Mittelstaedt, Axel. Psychiatrische Universitatsklinik, Rhein. Landeskrankenhaus, 4 Dusseldorf, Germany /Controlled long-term study on senile hypertension./ Kontrollierte Langzeitstudie bei Altershochdruck. ***Arzneimittel-Forschung (Aulendorf/Wurtt).*** **20(10):1542-1545, 1970.**

The results of a controlled, long-term study of senile hypertension are presented. Ten inpatients suffering from hypertension of slight, medium or severe degree, and from organic brain syndromes were treated with Combipresan, a combination of 2-(2,6-dichlorphenylamino) -2-imidazoline hydrochloride (Catapresan) and 1-oxo-3(3-sulfamoyl-4-chlorphenyl) -3-hydroxy-isoindoline (chlortalidon), for a period of 13 to 14 weeks. The study aimed at determining whether a long existant hypertension, already pretreated, could be influenced favorably without detrimental side effects of a physical and psychopathological nature. Along with an extensive drop of blood pressure, no deterimental influence on the psychopathologic condition of the patients was observed. The side

effects were only slight and temporary. 4 references. (Author abstract modified)

090070 No author. Author address not given Galveston County study shows tranquilizers surpass aspirin as medicinal poisoning agents. *Texas Medicine.* 66(7):99, 1970.

The chief culprit in most accidental poisonings in Galveston County, according to a survey, was medicine. A retrospective analysis of data from 4 major county hospitals during 1963 to 1968, including name, age, sex, date of poisoning, and general diagnosis, was performed by an IBM 1800 computer. Results showed tranquilizers surpassed aspirin as the leading medicinal poisoning agent, followed by barbiturate and nonbarbiturate sedatives. Medicinal agents were involved in twice as many poisonings in 1968 as in 1963. The rate of self-induced poisoning by drugs, especially among women, rose sharply, and was most common in the 20 to 30 year old age group. The other leading agents involved in poisonings were: cleaning and polishing agents, pesticides, gases and vapors. Accidental poisoning was a special problem with children 1 to 3 years old and represented a failure on the part of adults.

090126 Ritter, G.; Grabner, F. Psychiatrische Universitatsklinik, v. Sieboldstrasse 5, D-3400Gottingen, Germany /Psychopharmacological agents and micturition disorders: cystometric investigations./ Psychopharmaka und Miktionsstorungen: Cystometrische Untersuchungen. *Nervenarzt (Berlin).* 41(5):232-234, 1970.

Twenty four patients of both sexes, aged 20 to 65 years, were treated with antidepressant and neuroleptic agents, and with tranquilizers. They developed micturition difficulties, e.g.,delayed or increased urinary frequency, nocturia, burning sensation during urination; one patient had an acute obstruction. Half of the patients presented no subjective complaints. The following observations were made during cystoscopic examination: hypotony of the detrusor muscle, 23 times; distension of bladder up to 2.5fold its normal capacity, with sphincteric hypotonia, 11 times; residual urine, 6 times. Infection of the urinary tract was noted in 4 cases. The symptoms are, therefore, based on functional disturbances of the voiding mechanism. 4 references.

090170 Maxwell, Susan; Massengill, Raymond, Jr.; Nashold, Blaine. Duke University Medical Center, Durham, North Carolina Tardive dyskinesia. *Journal of Speech and Hearing Disorders.* 35(1):33-36, 1970.

Only recently has tardive dyskinesia been recognized as a distinct clinical entity. Evidence supporting the opinion that psychotropic drugs, especially phenothiazines, are responsible for the tardive dyskinesia syndrome is accumulating. It is believed that speech pathologists as well as physicians will be seeing more and more patients with tardive dyskinesia for differential diagnosis and therapy. Two case histories exemplifying definite characteristics of this condition (slurred speech, 'tongue thrust', some ataxia) are reported and discussed. 6 references.

090359 Guillan, Ramon A.; Zelman, Samuel; Reinert, R. E.; Smalley, Robert L. Laboratory Service, Veterans Administration Hospital, Topeka, Kansas Electron microscopy. Sudden death in patients under phenothiazine therapy: study of three cases. *Journal of the Kansas Medical Society.* 71(6):213-218, 1970.

Sudden death in phenothiazine therapy with clinical and postmortem characteristics of cyanosis, extreme passive congestion, edema, and parenchymal pulmonary hemorrhage (appearances characteristic of acute hypoxic death) was investigated with the electron microscope (EM) and cardiac tissue of 3 patients who died in such a manner. Light microscopy failed to disclose changes which could explain sudden death. In EM examination, 2 control hearts showed well preserved mitochondria andwell formed cristae; in the study cases, however, mitochondrial abnormalities comprised swelling and irreversible structural changes such as loss of parallel 'unit membrane' configuration, vesiculated cristae with granulations, and a roughly granular or filamentous matrix with osmiophilic masses. Myofibril degeneration was also noted. Although similar changes have been described in other types of heart disease, the known inhibition of mitochondrial respiration and respiratory center depressant action of the phenothiazines indicates a direct action of these drugs upon mitochondrial organization of the heart. 20 references.

090366 Monro, Pauline. Atkinson Morley's Hospital, Copse Hill, Wimbledon, London S.W.20., England Iatrogenic encephalopathy. *Postgraduate Medical Journal.* 46(535):327-329, 1970.

A 36 year old female with a history of rashes and exfoliative dermatitis while on treatment with sulfonamides was admitted with symptoms of fear, panic attacks, and palpitations. Treatment consisted of 1200mg dichloralphenazone, 500mg triclofos, and 25mg chlorpromazine every 4 hours. Fever, rash, facial edema and involuntary twitching began on the eighth day, followed 5 days later by neurological and systemic disturbances. Various clinical tests conducted included blood studies, ESR, plasma urea, serum electrolytes, serum aspartate transaminase, serum alanine transaminase, lever function tests and cerebrospinal fluid lymphocytes. Electroencephalograms were also taken. The rash was treated with phenergan and piriton for 4 days, and intramuscular hydrocortisone was given for 8 days after the onset of stupor, starting at 400mg/day. The encephalopathy was attributed to a delayed allergic reaction to drugs. Both chlorpromazine and sulfonamides may be broken down to the same quinone ring, which may form an allergen, thus resulting in cross-sensitization between the 2 drugs. 14 references.

092211 Boulton, Alan A.; Cookson, Brian; Paulton, Richard. Psychiatric Research Unit, Univ. Hospital, Saskatoon, Saskatchewan, Canada Hypertensive crisis in a patient on MAOI antidepressants following a meal of beef liver. *Canadian Medical Association Journal (Toronto).* 102(13):1394-1395, 1970.

A patient being administered a monoamine oxidase inhibitor (MAOI) type of antidepressant for chronic neuroses experienced hypertensive symptoms after eating beef liver rich in p-tyramine. The case history is described, and results of laboratory investigations of the tainted meat are discussed. Psychiatric patients being maintained on MAOI drugs should be warned not only of the danger of consuming foods rich in p-tyramine and other amines, but also of the danger that some foods may give rise to high amine levels as a result of bacterial contamination or the aging process, or both. 13 references.

093445 Chase, Thomas N. Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014 Drug-induced extrapyramidal disorders (Unpublished paper). Bethesda, Maryland, NIMH, 1970. 37 p.

Drug induced extrapyramidal disorders are reviewed, and the relationship of pharmacologically induced extrapyramidal syndromes to the functional state of central dopaminergic transmission is examined. The discussed extrapyramidal syndromes produced by drugs include: akathisia which occurs in about 10% of patients receiving neuroleptic therapy; acute dyskinesia (acute dyskinetic reactions occur in about 5% of patients receiving neuroleptic therapy --most commonly in children and young adults); parkinsonism (the estimated incidence in patients receiving neuroleptic drugs is about 10%); and tardive dyskinesia which occurs in about 15 to 25% of patients receiving neuroleptic therapy. Neuropathologic findings in the syndromes are reviewed. The effect of amine active drugs on extrapyramidal function are reviewed for: reserpine, tetrabenzine, alpha-methylparatyrosine, synthetic belladonna alkaloids, L-dihyroxyphenylalanine (L-dopa), apomorphine, phenothiazine derivatives and butyrophenone derivatives. Drug induced extrapyramidal syndromes may be classified according to their response to amine active compounds. The effect of amine active drugs on pharmacologically induced extrapyramidal disorders is reviewed in relation to this classification. Finally, studies on the effect of L-dopa, alpha-methylparatyrosine, and neuroleptic agents on central dopamine metabolism in man are reviewed. 113 references.

095020 Skarbek, Andrew. The Langham Clinic of Psychotherapy, 37 Queen Anne Street, London, W. 1, England A psychophysiological study of breathing behavior. *British Journal of Psychiatry (London).* 116(535):637-641, 1970.

Changes in resting breathing rate (RBR) of 101 acute psychiatric patients during the course of treatment in hospital have been measured. Clinical improvement was significantly associated with a mean decrease of RBR of 3.40 breaths per minute. Treatment with phenothiazines appeared to decrease RBR, while electroconvulsive therapy and to a lesser extent antidepressants appeared to increase it. There were no statistically significant differences between diagnostic groups in degree of change of RBR. 8 references. (Author abstract)

095410 Dembicki, Eugene L. author address not given Psychiatric drugs and trends. *Journal of Psychiatric Nursing and Mental Health Services.* 8(4):38-39, 1970.

The side and toxic effects, contraindications, and dosage of the phenothiazines are described.

Although side effects are varied and more pronounced with some products than others, drowsiness is one of the most common. Other side effects include blood dyscrasias, jaundice, permanent liver damage, Parkinsonlike condition, and transitory postural hypotension. Phenothiazines should be used with caution in patients with arteriosclerosis or cardiovascular disease and are definitely contraindicated in comatose states caused by central nervous system depressants or patients under the influence of barbiturates, alcohol, or narcotics. The dosage administered orally, rectally, intramuscularly, or intravenously, must be individualized. There should be steady increases until symptoms are controlled or side effects become troublesome, at which time dosage may be reduced to a maintenance level. Often large dosage levels for months are necessary to improve resistant mental and emotional disturbances.

095443 Whitlock, F. A.; Nadorfi, M. I. University of Queensland Department of Psychological Medicine, Royal Brisbane, Queensland 4029, Australia Diethylpropion and psychosis. ***Medical Journal of Australia (Sydney).*** **2(23):1097, 1970.**

A case history is presented to demonstrate some of the diagnostic difficulties associated with diagnosing the particular form of drug induced psychosis resulting from treatment with diethlpropion of patients who had taken amphetamine and/or phenmetrazine before being treated with the appetite suppressant. The patient, a 26 year old female, was admitted with an original diagnosis of schizophrenia. She had been treated with amphetamine in the past and had been taking an antihistamine, avil. Preadmission behavior, diagnosis and treatment are discussed; in addition, later admissions following suicide attempts with chlorpromazine or avil are noted. It is concluded, from this case and similar ones, that young female patients of unstable personality and who have taken amphetamine or related substances to excess in the past are peculiarly susceptible to effects of overdosage of diethylpropion. 6 references.

097999 Blum, A.; Mauruschat, W. Psychiatrische u. Neurologische Klinik der Freien Universitat Berlin -- Psychiatrische Klinik II. Berlin, Germany /Temperature increases under treatment with psychopharmaceuticals./ Uber Temperaturanstiege unter der Therapie mit Psychopharmaka. ***Psihofarmakologija 2: Radovi Drugog Jugosl. Psihof. Simpozija -- 1969.*** **Zagreb, Medicenska Naklada, 1970. 441 p. (p. 125-132).**

Temperature increases with neuroleptic therapy are reported. The neuroleptics tested were: the dibenzodiazepine derivative HF-1854 (211 patients); the benzothiazepine derivative clothiapine wander-2159 (52 patients); and the phenothiazine derivative perazine (55 patients). With the first 2 neuroleptics, temperature increases over 38 degrees C were found significantly more frequently than in the untreated group of control Ss, and no significant temperature increases were found with perazine. With HF-1854, the temperature increases were found to coin- cide with accelerated sedimentation rates and changes in the blood white cell count to significant degreee. At the same time, the patients so treated were subject to upper respiratory disorders. Male patients revealed a higher incidence of hyperthermia than females in response to HF-1854. The question as to the origin of hyperthermia in response to psychopharmaceutical drugs is discussed. The 2 possibilities considered are: centrally conditioned regulation disturbances, or disturbances due to immunological resistance. 16 references. (Author abstract modified)

098022 Bente, D. Nervenklinik der Universitat Erlangen - Nurnberg, Germany /Population dependent differences of central nervous reactivity to neuroleptics./ Populationsabhangige Unterschiede der zentralnervosen Reaktivitat auf Neuroleptika. ***Psihofarmakologija 2: Radovi Drugog Jugosl. Psihof. Simpozija -- 1969.*** **Zagreb, Medicenska Naklada, 1970. 441p. (p. 95-99).**

Reference is made to a previous comparative investigation of dif- ferences in response to neuroleptic medication among different populations. These populations, comprising paranoid hallucinating schizophrenics in Erlangen and in New York, were evaluated for reactivity to butaperazine medication. Although no significant difference was found in the therapeutic response, the side-effects of extrapyramidal motor disturbances revealed significant differences between the 2 groups. Differences in the quantitative analysis of EEG tracings also revealed changes in the cerebral reactivity in the 2 groups. This was observed in the variable resistance against the quenching effect of the neuroleptic, which produces greater extrapyramidal side-effects in patients with marked alertness. Although

the explanation for the different responses in different populations isnot clear, it is suggested that a significant difference exists between populations in biogenic amine metabolism which regulates the central nervous system activity. 10 references. (Author abstract modified)

100016 Kirk, L.; Rasmussen, K.B.; Faurbye, A. St.Hans Hospital, Department D, 4000 Roskilde, Denmark Retinopathy following thioridazine treatment. *Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).* No.217:56, 1970.

Four new cases of pigmentary retinopathy in patients treated with thioridazine are presented. Three of the patients had a dose of thioridazine of 300-500mg/24 hours and the last patient received thioridazine 150mg/day. The term pigmentary retinopathy is perhaps misleading, because it is a degeneration of the layer of rods and cones and the pigmented layer. Previously reported and present cases are all in older female patients with mean age 57 years (from 47 to 73 years). It is suggested that this group of patients represent a higher risk group of this drug complication, just as the same group of patients more often get persistent dyskinesia under phenothiazine treatment. (Author abstract modified)

100083 Thomsen, Klaus. Psychopharmacological Research Unit, Arhus State Hospital, 8240 Risskov, Denmark Lithium-induced polyuria: experimental studies in man and the rat. *Acta Psychiatrica Scandinavica (Supplement) (Kobenhavn).* No.217:28, 1970.

During treatment of manic-depressive patients with lithium, polyuria occasionally develops; in some cases the urine volume may amount to 6-8 liters per day. This side effect has been studied experimentally in rats. The animals were given fodder to which lithium has been added in sufficient amounts to produce a serum lithium level around 0.7milliequivalents per liter; this could be maintained for months. Within 2 weeks the urine volume rose from the control level of about 100ml/kg body weight per day to a constant level around 700ml/kg per day. This was not accompanied by any change in either the creatinine clearance or the lithium clearance. Administration of 15 units/kg body weight of vasopressin counteracted the polyuria wholly or partly within the first 3 weeks, but thereafter the polyuria was resistant to vasopressin. The lithium induced polyuria was not all stages fully reversible. Studies on patients have confirmed that lithium induced polyuria is not accompanied by any change in either the creatinine clearance or the lithium clearance; the appearance of polyuria therefore need not lead to any change in the maintenance dosage of lithium. (Journal abstract)

100511 Solzman, Carl; Shader, Richard I.; Pearlman, Michael. Psychiatry Department, Massachusetts Mental Health Center, Harvard Medical School, Boston Psychopharmacology and the elderly. *In: Shader, R., Psychotropic drug side effects.* Baltimore, Williams & Wilkins, 1970. 290 p.(p.261-279).

The use of psychotropic drugs in treating elderly patients is discussed. It is stressed that the elderly patient who requires psychiatric medication brings a host of complicated physical and emotional factors to the treatment situation. By virtue of the natural aging process, his body may be less capable of absorbing a drug, distributing it, reacting to it, and excreting it. He may be increasingly sensitive to drug effects and side effects and require a lower dose, or he may hardly respond at all. As a result of pathological processes more common in older persons, the patient's natural ability to cope with psychiatric medication may be further compromised. Medication that he may be receiving to ameliorate medical problems may interact with psychiatric drugs thereby producing either antagonism or synergism between them. Nevertheless, psychotropic drugs are effective in a variety of psychiatric conditions common to the elderly. The physician must take care, however, to select his drug of choice as much on the basis of possible deleterious side effects as upon presumed therapeutic efficacy. Careful medical evaluation should be obtained before psychotropic drug prescription is initiated. Dosage must be adjusted to the status of the individual patient and not necessarily reduced below that given to younger patients. Throughout the course of psychiatric drug treatment, the patient's medical status as well as his mental status must be monitored. Lastly, careful prescription of psychiatric drugs is particularly important in the elderly, since there is likely to be less tolerance to the effects and side effects of such drugs. 75 references. (Author abstract modified)

100512 Shader, Richard I.; DiMascio, Alberto. Psychiatry Department, Massachusetts Mental Health Center, Harvard Medical School, Boston

Galactorrhea and gynecomastia. *In: Shader, R., Psychotropic drug side effects.* Baltimore, Williams & Wilkins, 1970. 290 p.(p.4-9).

In a discussion of the effects of psychotropic drugs on endocrine and metabolic functions, specific emphasis is placed on the development and treatment of the conditions of galactorrhea and gynecomastia. Gynecomastia in males may occur from increased secretion of luteotropic hormone through its direct effect on mammary tissue or from the effects of increased gonadotropic hormones on the production of estrogen by the testes. Nonpuerperal galactorrhea and gynecomastia are well established as common sequelae following administration of a variety of psychotropic drugs. Galactorrhea probably occurs with all compounds which suppress the secretion of the prolactin inhibitory factor in the hypothalamus. The clinician, however, should keep in mind other possible causes of both conditions. When related to the psychotropic drugs, galactorrhea usually occurs with long duration, high dose, phenothiazine regimens and is often accompanied by amenorrhea. Dose reduction is usually sufficient treatment, although it is occasionally advisable to switch to another drug. Gynecomastia in males is infrequent and should be similarly treated. 38 references.

100513 Shader, Richard I. Psychiatry Department, Massachusetts Mental Health Center, Harvard Medical School, Boston Adverse reactions. *In: Shader, R., Psychotropic drug side effects.* Baltimore, Williams & Wilkins, 1970. 290 p.(p.1-3).

An introductory statement is presented to a volume on psychotropic drug side effects. It is emphasized that because of confusion in terminology, a distinction must be made between side effects and adverse reactions. Problems in precise definition of side effects are briefly noted. Several suggestions are made for clinical procedures to safeguard against undesirable reactions to psychotropic drugs, and for effective evaluation of the nature of such conditions when they exist.

16 METHODS DEVELOPMENT

090358 Lauter, H. University Clinic for Nervous Diseases, Gottingen, Germany Lithium treatment of the psychoses. *German Medical Monthly (Stuttgart).* 15(4):230, 1970.

The availability of lithium preparations for long-term therapy for manic-depressive psychosis and the determination of blood lithium levels is discussed. Long-term treatment of manic-depressive psychoses is presently treated by Quilonum (536mg/tablet) and Hypnorex (400mg/ tablet). A serum concentration of 0.8mEq/l has been found to be a minimal blood level for prophylactic effects; the daily dose depends upon the rate of excretion. Flame photometry is the common means of measurement, although this may also be accomplished with absorption spectography. For the first few weeks of treatment, estimations must be made every 8 to 14 days. As soon as the desired lithium concentration has been reached and it remains constant for 2 or 3 successive estimations, the interval between examinations can be lengthened to 6 to 7 months. Thereafter, serial examinations are necessary only: (a) if signs of intoxication appear, b) in the presence of intercurrent diseases, c) if the lithium dose is altered, and d) if the manic -depressive psychosis reappears.

092102 Downing, Robert W.; Rickels, Karl. author address not given The prediction of placebo response in anxious and depressed outpatients. *In: Wittenborn, J., Psychopharmacology and the Individual Patient.* New York, Raven Press, 1970. (p. 160-188).

A form of stepwise multiple regression analysis is used in an effort to select a sufficiently large number of relevant variables to predict the response to placebo treatment in a large group of neurotic patients participating in double blind drug trials in several diverse treatment settings. In the study, 73 regressors generated from a set of 30 patient, illness, and doctor variables were used as independent variables in a multiple regression procedure in an effort to identify significant predictors of 3 measures of placebo response. The study sample consisted of 388 neurotic outpatients treated in either clinic or private practice settings. They had been assigned in accordance with a double blind procedure to placebo treatment in several studies investigating the effectiveness of either minor tranquilizers or antidepressants. Conservatively estimated, 28% of the variance in placebo response was accounted for by the full set of regressors, and 19% by a reduced set of predictors derived from a stepwise search procedure. Lower social class affiliation and its concomitants, favorable physician prognosis, acuteness of illness, and lower initial depression were

found to predict all 3 measures of placebo response. The additional factors identified as predictors and the improvement measures with which they are related are presented. 21 references. (Author abstract modified)

096196 Dembicki, Eugene L. author address not given Review of the phenothiazines (part I). ***Journal of Psychiatric Nursing and Mental Health Services.*** **8(3):36-37, 1970.**

Phenothiazines, used in medicine for their tranquilizing effects, are described and the principal phenothiazines developed in the 1950 to 1960 period are listed. Stability and potency of the several phenothiazines listed vary although the compounds all have the same basic phenothiazine nucleus. Primary pharmacological effect of the phenothiazines is their apparent depression of the subcortical area of the brain without impairing the higher cortical functions. The drugs are believed to act primarily on the neural centers in the general area of the diencephalon, selectively inhibiting the hypothalamus. The phenothiazines are widely used clinically, particularly in treating symptoms of psychomotor agitation, senile and arteriosclerotic psychoses, obsessive and phobic reactions, schizophrenia, manic-depressive states, melancholia, paranoid psychoses, hysteria, and in mitigating the acute withdrawal symptoms of drug addiction and alcoholism.

098069 Alapin, B. Institut Psychoneurologique, Pruszkow, Poland /The importance of cybernetics for psychopharmacology./ L'importance de la cybernetique pour la psychopharmacologie. ***Psihofarmakologija 2: Radovi Drugog Jugosl. Psihof. Simpozija -- 1969.*** **Zagreb, Medicenska Naklada, 1970. 441p. (p. 89-94).**

The cybernetic method, which has already proven useful to psycho- pharmacology, is exemplified in the work of Vinar, who has proposed a method for the selection of psychotropic medication by this means. This method is based on the determination of a number of clinical symptoms together with EEG determinations, which can be standardized for various drugs and applied to new patients according to their symptoms. In order to elucidate the mechanism involved in drug action in humans, one plan is to analyze such findings in a large number of cases where a well defined symptom has disappeared following the administration of a given drug. The most cogent data in this analysis would be the difference in composition of the arterial and venous blood of the brain. A second factor in this analysis may be the EEG results, and a third one could be derived from the examination, in animals, of the drug effect on the chemistry of relevant brain structures. 4 references.

17 MISCELLANEOUS

090365 Miller, Russell R.; DeYoung, Dirk V.; Paxinos, James. Box 96, University of Chicago Hospitals and Clinics, Chicago, Illinois 60637 Hypnotic drugs. ***Postgraduate Medical Journal.*** **46(535):314-317, 1970.**

Use of hypnotic drugs is indicated in treating acute and chronic insomnia. Onset of action is rapid with liquid preparations of chloral hydrate, pentobarbital and secobarbital, but these drugs are more conveniently given as capsules, where drowsiness occurs within 30 minutes. Duration of hypnotic effect depends on the intrinsic pharmacodynamic characteristics of the drug and the dosage used. Ultra-short-acting barbiturates, such as sodium hexobarbital, sodium methohexital and sodium thiopental are useful in treating patients who have difficulty only in falling asleep. To induce and maintain sleep, a dose of 1.0to 2.0g chloral hydrate is indicated. Dose variability among patients depends on differences in metabolism, in central nervous system response, and on the degree of anxiety or depression present. Treatment is therefore begun with a low dose (0.5g chloral hydrate or 50mg secobarbital or pentobarbital), which may be doubled or tripled if hypnosis is not achieved. Common side-effects include residual sedation and allergic reactions. Tolerance to, and physical dependence upon barbiturates and most non-barbiturates is noted. Interaction of hynotics with alcohol, tranquilizers, calcium salts, mephenesin and thiamine can occur. Barbiturates are contraindicated in acute intermittent porphyria, and in some cases of hepatic disease and pregnancy. 13 references.

090428 Daniel, R. Wolston Park Hospital, Brisbane, Queensland, Australia Psychiatric drug use and abuse in the aged. ***Geriatrics.*** **25(1):144-145, 148-151, 154-155, 158, 1970.**

It is still not fully appreciated by many physicians that mental symptoms of confusion in the elderly may result not only from a chronic brain syndrome but often are caused by an underlying physical illness, commonly cardiac and respiratory illness. There is often great difficulty in differentiating an acute confusional state from chronic brain syndrome. Since there is no single test which will accomplish this, it is important that patients be given a thorough physical examination. Use of tranquilizers undoubtedly controls agitation, but it is more important to treat the disease as a whole, rather than a symptom. The monoamine oxidase inhibitors have come under fire in the last few years as unsafe under certain conditions. One of the difficulties in prescribing these drugs is that the patient's depression may not respond, and it is then necessary to try an iminobenzene derivative. Unless the former drug is halted for 10 days prior to new medication, severe hypertension may result. It is uncertain whether electroconvulsive therapy is dangerous in the aged. Although most authorities agree that is is reasonably safe for severe depressions, it seems that iminobenzene derivatives should be tried first in most cases. There has recently been a great deal of publicity regarding the effective use of cerebral arterial dilators in cerebral arteriosclerosis. Until simpler and more practical methods are devised to measure cerebral blood flow, it is difficult to pronounce for or against these drugs. A common misuse of the phenothiazines is to try to relieve neurotic reactions and depressions. The biggest therapeutic error when using these drugs is using too small a dose when a large dose is essential. The danger of using barbiturates as sedatives is that insomnia is often treated as a disease rather than as a symptom. The drug depresses respiration, causing pulmonary hypoxia resulting in cerebral anoxia with cerebral irritation and restlessness. As well as administering drugs, it is important to mobilize patients. Medication should be strictly supervised, because some patients are experts in not taking tablets. 5 references.

091208 Hiebert, J. Mark Sterling Drug, Inc., New York, New York Governmental regulation of the drug industry. ***Cleveland State Law Review.*** **19(1):37-42, 1970.**

A paper on governmental regulation of the drug industry was presented at the American College of Legal Medicine's 1969 convocation. It emphasizes the importance of the drug industry to modern society. The drug industry should not abdicate its responsibility to regulatory agencies. It is felt that government and industry should cooperate by communicating with each other and agreeing on a common goal.

093085 Kibrick, Eleanor; Smart, Reginald G. Addiction Research Foundation, Toronto, Ontario,

Canada Psychotropic drug use and driving risk: a review and analysis. *Journal of Safety Research.* 2(2):73-85, 1970.

A review and analysis are made of psychotropic drug use and driving risk. The studies reviewed are of the incidence of psychotropic drugs in general populations, in samples of drivers, and samples of accident drivers. Investigations have varied in terms of drugs studied, reliability of data collection procedures and criteria for choosing sample populations. This variability plus lack of replicative investigations makes the generation of conclusions tentative at this time. The studies cited did show that as high as 35 to 50% of the general population risk driving after drug use at least once per year and suggest that 11 to 15% of accident drivers have taken a psychotropic drug prior to their accident. Psychotropic drug use is most likely to be found among certain drinking driver groups, especially the fatally injured. It is indicated that the veracity of drivers' statements about drug use is very low and drug use estimates derived from questioning are probably very conservative. Further research is recommended in associating the use of psychotropic drugs with driving errors or with responsibility for accidents. 58 references. (Journal abstract modified)

097621 Abuzzahab, F. S., Sr. College of Medical Sciences, University of Minnesota, Minneapolis, Minnesota Clinical psychopharmacology: conceptual models of current trends. *Postgraduate Medicine.* 48(4):189-195, 1970.

Simple, descriptive classifications helpful in predicting psychopharmacological drug responses are presented. Specific drugs, alone and in combination, are tabulated under subdivisions of the anxiety and depression syndrome. Minor tranquilizers are categorized chemically. Schizophrenia is classified, and specific drugs associated with each classification are given. The extrapyramidal side effects are grouped as: akinesia and dystonia; and, akathisia and tremor; for which drugs are given by type, whereas a third category, rigidity or tremor, is referenced to the antiparkinsonian drugs which are classified by specifics and by type. The affective psychoses are categorized and are related to drugs by type, specific drugs, and electroconvulsive therapy. Tabular data is discussed. 21 references.

098033 Goldwurm, G. F.; Cattaneo, M. L.; Cocchi, A. Istituto di Clinica Psichiatrica del' Universita degli studi di Milano, Milan, Italy /Some observations on the dynamics of the destructuring of delirium during pharmacotherapy./ Quelques remarques sur la dynamique de la destructuration du delire pendant le traitement pharmacotherapeutique. *Psihofarmakologija 2: Radovi Drugog Jugosl. Psihof. Simposija -- 1969.* Zagreb, Medicenska Naklada, 1970. 441 p. (p. 113-117).

It is the general opinion that the specific indication for the neuroleptic drugs is for treatment of paranoid schizophrenia, chronic hallucinatory delirium or the paraphrenias, and that they may be used with some success for delirium in another context. According to some authorities, the action of these drugs is not only confined to the relief of symptomatology, but is also relevant to the repair of certain structures related to the psychotic process. It is important to recog- nize the role fo the delirium in the organization of the psychopatho- logical personality, whether with psychic disaggregation (schizophrenia) or without it (chronic delirium). The structuring of the delirium and the destructuring during pharmacologic therapy, mainly the trifluopera- zines and butyrophenones (haloperidol), is discussed. The manner in which the signs of delirium disappeared was characterized by a rapid crisis in a small number of cases and by a slow subsidence in the majority of them. Signs of disaggregation of personality tended to regress. Some of the features of psychoanalytic technique, such as transference, have also been noted during pharmacotherapy. During the remission from delirium, it is important that the patient be surrounded by reassuring persons including the physician and the family. The psychopharmacodynamic mode of action may be either directly on the agitation or anxiety, and only secondarily on the delirium and hallucinations, thus making it possible for the application of therapy; or, directly upon the hallucin- ations and delirium by the destruction of the psychopathological organ- ization of the personality. 8 references.